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Julius Bertram
September 1887

HYDROPHOBIA

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HYDROPHOBIA

AN ACCOUNT OF

M. PASTEUR'S SYSTEM

CONTAINING

A TRANSLATION OF ALL HIS COMMUNICATIONS ON THE SUBJECT, THE TECHNIQUE OF HIS METHOD, AND THE LATEST STATISTICAL RESULTS

BY

RENAUD SUZOR

M.B., C.M. EDIN. & M.D. PARIS

Commissioned by the Government of the Colony of Mauritius to study M. Pasteur's new Treatment in Paris

WITH SEVEN ILLUSTRATIONS

London

CHATTO & WINDUS, PICCADILLY

1887

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TO

HIS EXCELLENCY

SIR JOHN POPE HENNESSY, K.C.M.G. &c.

GOVERNOR OF MAURITIUS

AND TO THE

HON. MEMBERS OF THE LEGISLATIVE COUNCIL

OF THAT COLONY.

In their zeal for the cause of science and of humanity, His Excellency moved, and the Members of Council unanimously voted, that a delegate should be appointed to study M. Pasteur's new treatment of Hydrophobia in Paris.

May that first example set by a small Colony not remain sterile.

The Delegate,

THE AUTHOR

PARIS: *July* 21, 1887.

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HYDROPHOBIA.

CHAPTER I.

A SHORT DESCRIPTION OF HYDROPHOBIA FROM THE EARLIEST TIMES DOWN TO THE END OF 1880.

SEVEN years ago, in 1880, rabies or hydrophobia had already been known, dreaded, and studied, in Europe, for more than 2,000 years. Countless authors had written upon it, beginning, so far as we can ascertain, with Democritus in the fifth century B.C., down to and including many living men of mark. Yet all our knowledge of it could be summarised in a very few pages. The disease, at first circumscribed, to all appearances, within a few limited geographical areas, had, with increasing facilities of intercommunication between nations, gradually spread to nearly every country of the globe, irrespective of latitude or longitude. It raged, with varying intensity, at all seasons of the year, and often assumed the proportions of an epidemic. It was occasionally met with in herbi-

vorous animals: the ox, the horse, the sheep; in swine and in birds more rarely; commonest of all in the carnivora: the cat, the fox, the jackal, the wolf, and the dog. It always originated in the latter—in what manner, spontaneously or otherwise, was not and is not yet known—and spread from them by contact and direct inoculation, by a bite oftenest, to the herbivora and to man.

The poison deposited in the wound lay incubative for a period varying from a few days to several months, and possibly even to several years. Then, having silently crept up and invaded the nervous centres, it suddenly broke out into a train of terrific symptoms, uniformly terminating in death about the fourth day, by asphyxia or by syncope, sudden stoppage of the heart. During that long and hopeless agony the patient's intellect kept clear and even brightened, and his affective sentiments became more vivid than ever, circumstances which all tended to add to the horror of the picture. Indeed, the very name of the scourge evoked in the popular mind in an unequalled degree the sombre image of fate, mysterious, awful, and inevitable.

Not all died who had been bitten by rabid animals, but only a certain varying proportion, as we

shall see later on by quoting a few figures. Those who escaped death still had to live for years with a feeling as of the sword of Damocles ever hanging over their heads, an uncertainty of life which led not a few to commit suicide.

As in all similar cases, everything had been thought of and used as remedial agents. In particular shall we refer to blood-letting *ad deliquium*, to exposure to a high temperature and excessive sweating, to mercury (Daniel Johnson, 1829), curare, electricity and revulsion all along the spinal column. Unfortunately, however, in the vast majority of reported cases of so-called cure by those or other means the diagnosis is far from unimpeachable. But on the other hand there is no doubt as to the efficiency of the preventive treatment first propounded by Celsus in the first century of our era, and than which none better had been devised up to our own day. He recommended, to sum up, the use, immediately after the bite, of free suction of the wound, then its thorough cauterisation by means of the hot iron. But seldom only could this treatment, in actual practice, be applied with sufficient boldness and thoroughness, or soon enough after the accident. And thus the percentage of deaths still ran very high.

Police regulations also, by diminishing the total number of dogs in a country, and by enforcing the better supervision of those that remained, contributed efficiently to lessen the number of casualties, as evidenced in the cases of Germany and of the Scandinavian peninsula, where the number of deaths from hydrophobia has gradually gone down from year to year until it is at present only counted by units.[1]

And yet, withal, small epidemics were ever and anon starting up afresh, and the malady retained intact all its old terrors. As the late Professor Bouley justly remarked, any positive knowledge we had gained in the general study of hydrophobia was limited to its causation, morbid anatomy, and history. The therapeutic phase had not dawned yet, and many thoughtful authors considered it as lying indefinitely beyond our reach. Experimental researches into the nature, the seat, and the properties of the virus of rabies had often been undertaken, but had only yielded very scanty results.

Somewhere about the year 1870 they were resumed with increased accuracy, not uninfluenced certainly by the lessons already taught by Pasteur on the micro-organisms and their importance in

[1] In Norway the dog-tax is about 12*s.* a year in the country. It is higher still in the towns.

pathology. Hallier, Klebs, and many others believed they had found the microbe of rabies. More recently Fol, of Geneva, and Dowdeswell, of London, announced a similar discovery. But the question is still unsettled and the microbe to be isolated. Numerous experimenters, in every country, tried inoculative experiments, and accumulated interesting although too often contradictory facts. Paul Bert ascertained that the substance of the salivary glands was always virulent, as also, to a high degree, the bronchial mucus. Nocard, of Alfort, dialysed the pure saliva of rabid dogs, and showed that its solid elements were always virulent and reproduced the disease when injected into healthy animals, while the liquid portion, similarly injected, remained inactive.

Brown-Sequard and Duboue insisted on the importance of the nervous element in hydrophobia, and the former calls it 'an ascending neuritis.' Magendie had already discovered that dogs could be rendered refractory to rabies as produced by dog-bites. He got a first mad dog to bite a second healthy one; this in turn when mad a third one, and so on. The periods of incubation became longer and longer, and the fourth or fifth dog failed to take the disease. That interesting fact remained useless and was soon completely forgotten. Galtier,

Galtier on rabbits

of Lyons, confirmed by Bouchard and others, showed that the lymphatic fluid was constantly virulent; the blood had long before been proved to be innocuous when injected into animals. The same author reproduced the malady in rabbits by inserting small pieces of the brain and medulla of rabid dogs under their skin. He for the first time studied hydrophobia in the rabbit, and found that: 'The rabbit in which rabies is developing itself remains quiet and low-spirited, often sleepy, more rarely agitated and frightened by the slightest sound. From the very outset there is well-marked weakness, sometimes localised in the first instance to the lumbar region, the hind limbs, and even the cervical region; soon it creeps and invades the whole body, and then it is gradually replaced by paralysis. All the movements of the animal are difficult, irregular, ill-defined, and soon become quite impossible. It walks in a sort of crawling way, the fore-limbs dragging the hind ones, which have become quite helpless. After the first few hours it is almost always possible to notice a series of contractions, sudden, convulsive, and frequent, in the limbs, the trunk, the cervical region, the muscles of mastication; in many cases there is also present an unceasing chewing movement.

General sensibility is gradually dulled and is sometimes quite lost, so that it becomes possible to thrust a pin into the animal without giving rise to any reaction on its part. Sight is lost or perverted, the eye becomes gradually less and less sensitive, the conjunctiva is congested, and the cornea, the aqueous and vitreous humours, dull and cloudy. Some of the animals groan and utter loud cries of distress if suddenly displaced or taken up by the ears or legs.

'The sense of taste appears to be also perverted, for they are seen swallowing fragments of straw and of fæcal matter, and to lick the floor of their cage.

'As a rule they do not try to bite. In one case, however, the animal had a tendency to do so, in particular when worried.[1] There is an abundant flow of saliva. Thirst and hunger have disappeared, or, when the subject tries still to drink or to eat, there soon supervenes a moment when deglutition is quite impossible.

'The circulation of the blood is irregular and the pulse beats from 109 to 200 a minute.

'The urine is scanty or is only expelled at the time

[1] A Russian laboratory assistant was actually bitten by a rabid rabbit. He had, however, been previously vaccinated, and remains well.

of death, so that the bladder is found after death to be at times full, at other times empty.' He concludes:

'1. Dog-madness can be transferred to the rabbit, which thus becomes a convenient and safe reagent enabling us to find out the virulence or non-virulence of various fluids taken from rabid animals. I have often used it in that capacity for the study of the different sorts of saliva (parotidean, submaxillary, &c.) and of a number of other liquids taken from rabid dogs, sheep, and rabbits.

'2. Rabbit-madness can be transferred to other animals of the same species; but I cannot as yet say whether the rabies-virus of the rabbit is equally virulent with that of the dog.

'3. The predominating symptoms of rabies in the rabbit are of the paralytic and convulsive types.

'4. The rabbit can survive from a few hours to one, two, three, and even four days, after the symptoms of rabies have clearly manifested themselves.

'5. Not only is the rabbit susceptible of taking rabies and of surviving a certain time after the malady has broken out, but it is also a constant fact, judging from my experiments, that the period of incubation is shorter in this animal than in any

other one; and this, I repeat, makes of it a most valuable reagent, enabling us to ascertain the virulence of this or that liquid.'

He then quotes twenty-five cases of experimental rabies in the rabbit giving an average incubation of eighteen days; also an experiment with salicylic acid, proving that that substance is quite inefficient—used by the hypodermic way—in preventing the development of the disease; and finally, he states that the saliva taken from a live mad dog, and kept mixed with water, was still virulent after twenty-four, and even thirty-six hours.

We may now give a short list of the main signs by which it is possible to make the diagnosis of rabies in the dog. The disease shows itself in one of two forms:—

1. Furious or delirious madness; by far the commonest.

2. Dumb madness.

In the furious form note:

(a) A change in the usual ways and habits of the animal. He becomes dull and voiceless, crouches down in dark and quiet corners. He tries to sleep, but is often disturbed in his sleep as if by painful dreams and delusions; he rises and walks about, then lies down again. He is in a continuous state

of restlessness and agitation. In some cases he is not agitated, but sleepy and careless of whatever is going on near him. If disturbed, he growls and shows no inclination to stir.

In either case he still obeys the voice of his master and has no tendency to bite yet.

The agitation increases. In his kennel he piles up the straw, lays his chest on it, then rises in anger and scatters the litter about. In apartments he tears and tosses the cushions, carpets, &c. Occasionally there is a manifestation of intense and unwonted attachment to some other animal, or to the people of the household; or he is seen constantly to lick cold objects (Delabere-Blaine). He is haunted by visions and hallucinations, he barks, snaps, and growls at imaginary beings (Youatt). But still he knows and obeys the voice of his master and has no tendency to bite him. Nevertheless, his saliva is already virulent, and his caresses dangerous. The saliva is virulent eight days, and possibly longer, before the disease is plainly evident.

Often, too, even in this early stage, dogs will bite a stick thrust at them. So also will they often bite people when worried but slightly.

(*b*) The mad dog has no horror of or repulsion for water. On the contrary, at all periods of the

malady he drinks eagerly or tries to drink. When he fails to swallow the water it is only owing to spasmodic contraction of his throat.

The appetite may be at first and for a short time increased. But very soon it diminishes and is quite lost and replaced by marked disgust for all kinds of ordinary food and a thorough perversion of the sense of taste. He tears everything that he meets, carpets, trees, grass, and swallows fragments of anything, including his own excreta, urine, earth, bits of straw, chips of wood, anything. As a consequence of this there is not unfrequently present a certain quantity of blood in the vomited matter, vomiting being a common phenomenon at this stage.

The saliva of the mad dog is not usually over-abundant, and may even be quite normal in quantity.

(*c*) The bark of the mad dog is quite characteristic, and is never forgotten when it has been heard once. Bouley says of it: 'Instead of bursting out with its usual sonority and of being made up of a succession of notes equal in duration and in intensity, it is hoarse, veiled, lower in tone, and after a first full-mouthed bark there follows immediately a succession of five, six, or eight howls coming far back from the throat and during which the jaws are never completely closed, as they are ordinarily

after each bark.' It is not unlike the voice of dogs chasing a hare; it is something intermediate between a bark and a howl, made up of the two, with something more added, strange and sinister.

(*d*) The sight of another dog at once and almost invariably puts the mad dog in a fit of passion. This is, therefore, an easy and valuable test method. The same effect is produced by the sight of a dog on all rabid animals, to whatever species they belong, including the sheep. Man alone perhaps constitutes an exception to the rule.

Renault quotes the case of a horse rendered rabid by inoculation from a sheep. This animal when shown a dog remained careless, but when a sheep—a healthy one—was brought in, he grew quite furious and tore it to pieces. This case stands solitary. This symptom has, of course, most value in the case of dogs which are naturally tame and non-aggressive in disposition.

The mad dog is analgesic, i.e., his general sensibility is blunted to a considerable degree. He now seems to feel only the very intensest pains. He no longer expresses pain by the usual nasal sound or the sharp cry which is so familiar. He can be beaten, pricked, and even slightly burnt, without stirring and without uttering any sound at all. If

severely burnt he moves to another place, but still remains mute although the face becomes expressive of pain. This fact explains the cases in which dogs which were later on ascertained to be mad were seen to bite and tear at their own limbs and bodies.

There is often present a certain degree of hyperæsthesia at the seat of the bite, if the dog has been bitten by a rabid animal, shown by his constant rubbing, licking, or biting of the part, the leg, the ear, on which, on examination, there is found nothing capable of explaining the facts observed, except, perhaps, a small cicatrix. The same phenomenon is often met with in other animals and in man, shortly before the onset of the disease.

The sexual instincts also are greatly excited and increased.

(*e*) *Confirmed Rabies.*—In a few cases the animal remains tame and unaggressive to the end, but as a rule he is in a state of delirious rage about which there can be no mistake as to its significance.

He bites and tears at everything thrown at him if he is chained or in a cage. He attacks furiously all animals that come within reach, later on man also, more rarely his own master. The pupils are dilated and the whole face bears an expression of terrible fierceness. Whilst biting and tearing he

is always *silent*, unlike the non-rabid dog who fights and barks all at once. He always, in preference, attacks animals rather than man. He often leaves home and wanders far away. From a distance he shows nothing peculiar, has his ordinary gait, and his tail instead of being held between the legs, as so often asserted, is kept high and wagging.

Later on, when tired, he walks with a tottering gait, the head low, the tongue hanging out of the mouth, covered with blood and dust, and the tail falling helpless. His sight, as well as his other senses, is now dulled, and he is much less dangerous. Still he can bite, however, and is to be dreaded. After wandering about for a few hours, or it may be days, he often comes home again. At last, on the fifth day or thereabout, emaciated and worn out by repeated attacks of fightful fury and the want of food, paralysed in the hind-quarters, he dies from sheer exhaustion and asphyxia.

Dumb-madness.—Inoculations of this form of madness often reproduce the disease in its furious form, and *vice versâ*, showing that the two are only different manifestations of one and the same malady. The stages *a*, *b*, *c*, are very much the same as in the furious type, perhaps less marked. Then, (*d*, *e*), the voice is quite lost, and even in the

first stages it is more exclusively a howl, with no admixture of the bark. The mouth is constantly gaping, owing to the paralysis of the lower jaw; the eyes open, without expression, constantly fixed in the same direction. The predominant symptoms are muscular weakness and cerebral depression. The animal is constantly lying down or sleepy, has neither the will nor the power to bite. His saliva is quite as virulent as in the other form.

In the immense majority of cases hydrophobia in the dog ends fatally; a few exceptional cases are, however, on record when the disease, spontaneously or under the influence of medical treatment—namely, submersion in cold water until asphyxia is nearly complete, bleeding, enemata—gradually disappeared and a cure was effected.

On *post-mortem* examination the main points of interest are the following: dark blue and almost black colour of the tongue and of the whole mucous membrane of the mouth. In the stomach some discoloration of the lining membrane, presence often of a black liquid, like coffee dregs; presence also of a collection of heterogeneous materials not usually swallowed by healthy dogs: hairs, straw, wood, coal, ashes, bits of carpeting, earth, &c. Blaine, Youatt, and others note this last sign in almost

every case; Bruckmüller, of Vienna, only in fifty-four per cent. of his observations.

Congestion of the lungs, of the central nervous system (Bruckmüller), extreme retraction of the bladder, are frequent but by no means constant or characteristic phenomena.

The duration of incubation is less than two months in more than eighty per cent. of the cases: very seldom longer than six months; eleven months in one case related by Youatt.

In the cat many of the symptoms of rabies forcibly recall to mind those we have already noted in the dog. It will therefore not be necessary to refer to them in detail, and it will be enough to add that this animal, like the wolf, very generally directs his attacks to the head and face. Wounds on those regions are particularly dangerous, as pointed out by all statistics.

The general precautionary measures best calculated to diminish the number of hydrophobic animals and to increase the security of the public from that terrible disease, are thus summed up by Bouley:—

1. Declaration to the authorities, by the proprietor, of any distemper in his animals, which can in any way be suspected of being rabies.

2. Immediate locking up of such animals, by the proprietor himself.

3. Destruction by the police of all rabid animals, and of all others bitten by such.

4. Compulsory locking up, under police supervision, and for a period of time not less than eight months, of all animals suspected of having been bitten by a rabid animal. Immediate destruction is always to be preferred, however.

5. All dogs constantly to wear round their neck a collar with their police number and the name and address of the proprietor.

6. All dogs left free to wander about, to wear an *efficient* muzzle.

7. All dogs to be stopped which do not fulfil the preceding two conditions.

8. Destruction of all dogs so stopped, after the lapse of a certain time, if not claimed. Such animals ought never to be sold or bought.

9. Male animals to be taxed more heavily than females.

10. Blunting of the teeth, so as to render the bites less virulent, like those of herbivorous animals whose teeth oftenest simply crush the tissues and do not penetrate them. (Bourrel).

In *man* hydrophobia assumes the same two

forms as in the dog—viz. the delirious and the paralytic, the former being by far the commoner of the two.

The delirious form can be subdivided into three stages:

(*a*) *Melancholia.*—Towards the end of the period of incubation the patient, whether he is aware of the impending danger or not, child or adult, becomes sad, taciturn, shuns all society. He suffers constantly from the intensest headache, and at night his sleep is disturbed by terrible dreams of very varied character. There are occasionally some itching or even painful sensations at the seat of the bite. This period is not always present, and seldom lasts more than four or five days. There is now also, in some cases, an irresistible impulse to walk or to run. In such exceptional cases of muscular excitement there is also found occasionally a state of mental irritability instead of the usual melancholy.

(*b*) *Excitement. Hydrophobia proper.*—The breathing becomes difficult, laboured. Inspiration is cut up by frequent sighs. Gradually all the muscles receiving their nervous supply from the medulla oblongata (the part of the nervous axis wherein the brain and spinal cord become con-

nected) become implicated, and there are produced the peculiar spasmodic contractions of the pharynx and larynx. General hyperæsthesia (or increased activity) of all the senses, horror of water and of all bright objects, of the lightest draught of air, of the slightest sound or smell. Convulsive fits. On the second or third day there supervenes the frequent symptom of 'sputation,'—the mouth, at first dry, now becomes moist and watery, filled with frothy mucus. There are frequent hallucinations of sight, of hearing. The voice is hoarse, convulsive, spasmodic, and may simulate the bark or howl of a dog. During the convulsive attacks the patient often hurts and bruises himself, and has still the tendency to run away from home. These attacks may alternate with fits of melancholia and manifestations of great despondency. The temperature rises, as in tetanus, and may still increase for one hour after death (Peter); up to 43° C. (Joffroy).

(c) *Paralysis* of all the senses, and finally of the intellect also, and death from exhaustion and paralysis of the respiratory and circulatory centres.

Hydrophobia in man can be confounded with hysteria, tetanus, epilepsy, delirium tremens, and certain forms of acute mania. It has sometimes been identified with uræmia or blood-poisoning from

kidney disease. It will be enough, in order to avoid confusion with the last-named affection, to remember that in hydrophobia the temperature rises as death approaches; in uræmia it always goes down below the normal. The type of the convulsions, the mental disorder, and the abnormalities of general and special sensibility, are very different in the two.

The paralytic form of rabies in man is much less common than the one just described. Nevertheless, in the second number of the 'Annales de l'Institut Pasteur,' Dr. Gamaleia, of Odessa, from whom is borrowed this description, publishes an account of about thirty such cases. He finds that they are generally the result of deep and multiple bites:

'Onset by a strong fever, general malaise and aching, headache and vomiting, as in all acute infectious diseases. Such an onset is very frequent also in cases of ordinary rabies. In all the patients whose temperatures were taken, there was found, at a certain period of the malady, a high degree of fever.

'Then come a train of localised pains, generally in the limbs bitten, and girdle pains at different heights of the vertebral column. These localised

premonitory pains are rare in the lower limbs (Brouardel).

'Next supervene a degree of numbness of the senses, fibrillar contractions, ataxy, paresis, and then paralysis more or less complete of the muscles first implicated. General sensibility remains intact, or, if it disappear, it does so very much later.

'Then the paralysis spreads, preceded or accompanied by sharp pain in the muscles invaded; the remaining limbs, the trunk, the rectum, and bladder, the face, the tongue, the eyes, are all paralysed. So also, sooner or later, and more or less completely, the respiratory centre, the implication of which brings about a marked change in the inspiratory phase of the patient's breathing, and, as a corollary, some difficulty in swallowing liquids (the so-called *great symptom* of *hydrophobia*, or horror of water, being a result much more of the imagination of the patient and of the medical man, than of the rabies virus).

'When well-marked, this respiratory lesion is the cause of dyspnœic convulsions in the muscles which are not yet paralysed. Then, frequently, return of the breathing to the normal, but spread of the paralysis to the heart and death by syncope.'

This form of rabies has a duration of seven days and a half on an average.

The same author concludes that the virus, from the study of the symptoms detailed, can only spread by the nerves, from the periphery or external surfaces to the centre. He also insists on the necessity of giving up the old notion of incurability of rabies when once developed, although he does not himself quote any authentic case of recovery, his main argument being based on the fact that rabies is not so common or so severe in its symptoms in man as in the dog, and yet there are on record cases of undoubted recovery in the latter animal. The medical man 'ought to cease aiding on the virus by morphia; he ought, on the contrary, to help the nervous system in its struggle against the all-invading virus, to assist the organism in bearing up against the momentary arrest of the vital functions (e.g. by artificial respiration).' In that train of reasoning hypodermic injections of strychnine might at any rate be tried.

On *post-mortem* examination the lesions of main interest are found to lie in the central nervous system. The nerve-cells are cloudy and granular: general congestion of the nerve-centres, the blood-vessels being dilated and ruptured here and there, giving rise to small hæmorrhages: miliary abscesses throughout the substance of the medulla oblongata.

more sparsely in that of the brain and cord; foci of finely granular matter infiltrating the normal nervous element, the peri-vascular lymph spaces and the walls of the blood-vessels which are compressed and assume a moniliform or beaded aspect; hyaline thrombi or blood-clots form in their interior at the level of those compressed points, the whole giving the appearance of a nodule or small tubercle in the interior of which Klebs thought he had discovered the specific micrococcus.

Ross, of Manchester, finds that the lesions are most marked around the central canal, but the anterior and posterior horns and the grey matter throughout is largely implicated also, mainly so perhaps. The same author draws attention to this interesting fact, that in tetanus and rabies the lesions are very similar, but that in the former case they are chiefly spinal, in the latter cerebral, in their main localisations (?). The ganglia of the sympathetic system and the nerve-roots show the same lesions as the brain and cord. The nerves, and in particular those of the part bitten, those rising from the medulla: the vagi, the glosso-pharyngeal, the hypoglossal, the spinal accessory, the phrenic, have been found red and hyperæmic, swollen, and the seat of minute foci of

hæmorrhage ;[1] the myelin is diffluent, fragmented, and in many nerve fibres the axis cylinder has altogether disappeared. (Wagner, Krukenberg, Cheadle.)

The lungs are red and congested, here and there the seat of small hæmorrhages, filled with frothy mucus formed at the time of death, for there were no auscultation signs of its presence during life. Very generally also some interstitial and subpleural emphysema. Those pulmonary lesions, just like the liquid venous-black state of the blood, seem to be the result of the terminal asphyxia (Brouardel).

Note also in some cases: hæmorrhages in the muscular tissue of the heart; parenchymatous nephritis; congestion and swelling of the lymphatic glands, with the terminal leucocythæmia; softness of the spleen and liver, the latter being in a state of fatty degeneration—all those forcibly remind one of the lesions found in other well-known infectious diseases, variola, scarlatina, septicæmia.

Incubation in Man.—Professor Brouardel quotes several trustworthy statistics, and in particular one in

[1] Portions of those nerves, inoculated, reproduce the disease. It would thus seem that the virus proceeded at first from the periphery to the centre, and secondarily from the centre to the periphery.

which, out of 170 cases, rabies showed itself within the first three months in 147 cases; and a second one in which 73 times out of 97 cases the disease declared itself within the same period. He concludes: 'Rabies supervenes oftenest in the course of the second month after infection; rarely after the third month, quite exceptionally after the sixth month.' The more numerous the bites, and the greater their gravity, the earlier do the symptoms appear. They manifest themselves earlier also in children than in old people.

From statistics drawn by Tardieu, Bouley, and the French Committee of Hygiene or Board of Health, as well as those published by medical men, the same author finds that after efficient and early cauterisation the death-rate amounts to 30 per cent. of the cases, rising to 80 per cent. in the cases where there was no cauterisation at all or where it was insufficient or tardy. The actual figures are slightly above those here mentioned. Efficient cauterisation is that effected by means of the hot iron, concentrated sulphuric, nitric, or carbolic acid, or the chloride of antimony and the acid nitrate of mercury, and applied less than one hour after the accident. Before applying the caustic it is often advisable to open up the wound well and

freely by means of a knife. Occasionally amputation of a finger or of a limb will have to be considered.

Under the age of twenty, 31 per cent. of persons bitten die of hydrophobia; the proportion rises to 62 per cent. above that age.

For wolf bites, Renault finds that, out of 254 individuals bitten, 164 died of hydrophobia, that is, about two-thirds. Dr. du Mesnil having collected accounts of over 800 cases of bites by mad wolves, found a death-rate from hydrophobia of 65 per cent.

For bites by mad dogs Renault gives the percentage of deaths as being one-third of the total number bitten. Statistics based on 383 cases collected by Bouley between 1862 and 1868, and by the Comité d'Hygiène from that date up to 1872 give a death-rate of 47 per cent. (180 out of 383).

Faber, in the kingdom of Wurtemberg, finds only 28 deaths out of 145 people bitten—i.e. 20 per cent. Some Viennese statistics give a death-rate of 11 per cent.; another counts 25 deaths for 125 cases. In Austria, in 1860, out of 115 persons bitten, 25 took hydrophobia—i.e. 22 per cent. Leblanc notes only five deaths out of 36 cases where the biting dogs had been diagnosed rabid at

the Alfort Veterinary School—15 per cent. In all those cases we are unfortunately not told how late after the accidents the tables were drawn up. If Bouley's figures seem to be perhaps too high, possibly because certain cases not followed by death were not reported, some of the other statistics, on the other hand, seem to remain below the truth.

The Comite d'Hygiène give the following figures for the years 1862–72:—

	No.	Deaths	Percentage
Bites on the face	50	44	88
,, hands	113	76	67·25
,, trunk	22	7	31·81
,, arms	40	12	30
,, legs	33	7	21·21
Multiple (face, hands, &c.) . .	8	6	
Total . . .	266	152	

Those figures do not give an exact expression of facts, but they are still of great use in indicating very fairly in what direction the truth lies.

Mr. Alfred Poland puts down the death-rate as being 1 in 4—i.e. 25 per cent.; Dr. and Mr. Gamgee say it varies from 5 to 55 per cent. Professor Gowers, in Quain's 'Dictionary of Medicine,' says: 'When no preventive measures are adopted, at least half,

perhaps two-thirds, of persons bitten escape. The immunity may be due partly to the bites being inflicted through clothes; partly to individual insusceptibility which has been found to exist in animals as well as in man.' These statements agree perfectly with those of the French authors.

As to the time of the year when rabies is commonest, it is sufficiently pointed out in the following table, published by Dr. Pasca, of Milan (1865) :—

June, July, August	14
March, April, May	35
December, January, February	14
September, October, November . . .	25

Such was the state, very briefly summarised, of our knowledge of hydrophobia, when in December 1880 M. Pasteur's attention was called by M. Lannelongue to the case of a little girl who was dying of that disease in his ward at the Hôpital Sainte-Eugénie.

M. Pasteur had now for many years been devoting his whole energies to the investigation of maladies confined almost exclusively to animals, and with what extraordinary amount of success most people have heard. They formed a necessary stepping-stone to the study of the more complex problems

of human diseases, for they left more scope for free experimentation and the acquisition thereby of great familiarity with such questions. The two classes of diseases, moreover, not unfrequently merge into one, being simply propagated from animal to man, and more or less modified in the latter. Experimentation, ingenious and critical, and an intuition of things, a manner of scientific conscience, developed to an unusual degree and suggesting the right choice out of many possible ones, added to which great perseverance and unshaken faith in results thus patiently come to, such are the main elements of M. Pasteur's strength.

A new era was now dawning in the history of hydrophobia, and more was done for it in the next few years than had been realised in the previous ages. Light was thrown upon many obscure points of its natural history; but, most important of all, the possibility of its prophylactic treatment in man, based on results already secured in animals in the analogous cases of splenic fever, the fowl-cholera, the swine-plague, and other maladies, was now announced for the first time. This early announcement was soon justified, and shown to be not only possible but probable, from the results of numerous experiments on dogs and other animals. In 1885

it was actually applied to the human subject. But we must not anticipate.

Those results were published in a series of communications made to the Académie des Sciences. They are so concise that we can do no better than translate them, only aiming in our rendering at being as faithful to the original as possible. We shall next give a detailed account of all we saw and learnt at the two laboratories of Rue d'Ulm and Rue Vauquelin, during our stay of many months at those two places, summing up with the statistics of all cases treated by the new method, and a few general remarks.

CHAPTER II.

M. PASTEUR'S COMMUNICATIONS ON HYDROPHOBIA.

I. *January* 24, 1881.—*On a New Malady produced by the Saliva of a Child who died of Rabies. Note by M. L. Pasteur, with the Collaboration of Messrs. Chamberland and Roux.*

This note deals with the experiments undertaken with the saliva of the child who died in Mr. Lamelongue's ward. This saliva, injected into dogs and rabbits, gave rise in them to a new and fatal disease, not to rabies. We shall, accordingly, not translate the article, although it is of great interest. M. Pasteur here expresses the idea that the new disease may possibly be the form assumed in animals by human rabies. A specific microbe had been isolated and cultivated. He foresees the possibility of vaccinating dogs against hydrophobia, and thus indirectly preserving man himself.

II. *May* 30, 1881.—The Academy may remember that we began the study of hydrophobia in the month

of December last, assisted by Messrs. Chamberland and Roux, whom M. Thuillier kindly joined.

By comparing the external symptoms of that malady with certain microscopical observations made on the brains of persons or animals who had died of hydrophobia, and by considering that it has not as yet been possible to communicate the affection by inoculation of the blood of rabid individuals, several authors were led to the belief that the central nervous system, and in particular the medulla oblongata, which joins the spinal cord to the brain and cerebellum, are specially interested and active in the development of the disease. This opinion was upheld with great distinction, two years ago, by Dr. Duboué. Nevertheless, the Lyons experiments leave room for much uncertainty as to the true seat of elaboration of the rabid virus.

'The rabid virus,' says the learned experimenter, 'exists in the saliva, as all know. But where does it come from? Where is it elaborated? . . .

'Hitherto I have only been able to detect the presence of the virus in the mad dog, in the lingual glands and in the bucco-pharyngeal mucous membrane.

'More than ten times, and always with the same want of success, have I inoculated the sub-

stance extracted by compression from the brain, cerebellum, and medulla oblongata of mad dogs.'[1]

I have the satisfaction of announcing to the Academy that our experiments have proved more successful. On several occasions, and often with success, we have inoculated the medulla oblongata, portions of the frontal lobes of one of the cerebral hemispheres, and also the cerebro-spinal fluid. The hydrophobia thus produced presented the usual period of incubation.

The virus of rabies is, therefore, not exclusively contained in the saliva. It is present also in the brain, where it is found to possess a virulence at the least equal to that of the saliva of rabid animals.

One of the greatest difficulties of researches on hydrophobia consists on the one hand in the uncertainty of the development of the disease after inoculations and bites, and, on the other hand, in the long duration of the incubative period—that is to say, of the time which lapses between the introduction of the virus and the appearance of the symptoms of rabies. It is torturing to the experimenter to have to wait whole months for the result of a single experiment when the question studied

[1] Galtier, *Bull. Acad. de Méd.*, Jan. 25, 1881.

requires very many such. Members will therefore undoubtedly be interested to hear that we have discovered a method for considerably shortening the duration of incubation of rabies and also of reproducing the disease with certainty.

That double result is secured by direct inoculation (after trephining the skull) on the surface of the brain of a healthy animal of the cerebral matter of a mad dog, taken out and inoculated in a state of purity.

The dog inoculated under such conditions shows the first symptoms of rabies in the course of one or two weeks, and death supervenes before the end of the third week. I may add that not a single one of the inoculations thus performed failed. So many dogs trephined and inoculated on the brain, so many cases of confirmed and rapidly developed hydrophobia. Considering the special characteristics of this method, one may foresee that the result will always be the same. The rabies developed has, furthermore, been sometimes dumb, at other times furious—that is to say, rabies under one or other of its two habitual types.

I conclude with this short exposition of facts, because our sole object to-day is to lay claim to the discovery of a new method of research, the

usefulness of which in practice all will apprehend.

III. *December* 11, 1882.—The study of rabies, of all diseases, seems to be the one which bristles with most difficulties. Clinical observation is powerless, and it is ever necessary to appeal to experimentation. But until yesterday the significance of the simplest experiment was wrapped up in undecipherable uncertainties.

The saliva was the only part where the presence of the virus of rabies had been detected with certainty.[1] But the saliva, inoculated by a bite or by direct injection into the areolar tissue, does not constantly give rise to rabies. Furthermore, when the malady does show itself, it is only after a prolonged incubation, the duration of which is both varying and unsettled.

It follows, therefore, that anyone wishing to draw conclusions from a set of experiments by inoculation, with regard to which no positive results have been come to, is always in fear of not having waited long enough for the results of his inoculation or else of having to deal with cases of absolute failure.

Add to this the difficulty of procuring the virus

[1] See Galtier, *Bull. Acad. de Méd.*, Jan. 25, 1881.

at will, the repulsion and danger of handling mad dogs, and it will be easily understood that the study of hydrophobia is full of mishaps.

The situation is no longer the same.

When I made up my mind, two years ago, to undertake a sifting study of that malady, I did not deceive myself as to the difficulties and slowness of the undertaking, and understood that the first problem to be solved consisted in finding a method of inoculation which would both reproduce the disease with certainty and do away with its prolonged incubation. Such a method we have discovered and explained in a note, which, in my own name and in the name of my fellow-workers, I presented to this Academy on May 30, 1881. It consists, on the one hand, in this fact, that the principal seat of the virus of rabies is in the central nervous system, where it is found in great quantity and where it can be gathered in a state of perfect purity, and, on the other hand, in this consideration, that the virulent matter inoculated pure on the surface of the brain after trephining developes rabies with rapidity and with certainty.

Since then we have found it quite as advantageous, although producing slightly different forms of rabies, to use another method, which is still

more simple in its application—namely, intravenous injection of the virus.

The two main obstacles to the experimental study of rabies had thus been got rid of.

The new investigations which I have the honour to communicate to the Academy to-day are still very incomplete, and yet, such as they stand, they are pregnant with suggestions of new views and new experiments. And, besides, to quote Lavoisier, 'a man would never give anything to the public if he waited till he had reached the goal of his undertaking, which is ever appearing close at hand and yet ever slipping farther and farther as he draws nearer.'

I think that my exposition of facts will gain both in clearness and in conciseness if I confine myself to the summing up of the results of our study. All details will be left aside for the present, and added later on as documents to the present communication.

1. Dumb rabies and furious rabies, or, to speak more generally, all forms of rabies, proceed from one and the same virus. We have, as a matter of fact, recognised that it is possible, experimentally, to produce furious rabies from dumb rabies, and inversely, dumb rabies from furious rabies.

2. Nothing is more varied than the symptoms of rabies. Every case of rabies shows, so to speak, its own train of symptoms, and there is every reason to believe that the special characters of any one case depend on the nature of the region in the nervous system, encephalon or spinal cord, where the virus has located itself and multiplied.

3. In the saliva of rabid animals the virus is found associated with various micro-organisms, and the inoculations of this saliva can give rise to death in one of three modes :

(*a*) By the new microbe which we have described under the name of 'the microbe of saliva.'

(*b*) By the excessive development of pus.

(*c*) By rabies.

4. The medulla oblongata of human beings, as also that of all animals who have died of hydrophobia, is always virulent.

5. The virus of rabies is met with not only in the medulla oblongata, but also in every other part of the encephalon.

It is also found localised in the spinal cord and, frequently, in all the parts of that organ.

The virulence of the cord, whether in its superior, middle, or lumbar regions, or even quite close to the cauda equina, is in no way inferior to the virulence

of the medulla or of the different parts of the encephalon (brain, cerebellum, medulla oblongata, pons, peduncles). The encephalon and cord continue virulent until the time when putrefaction sets in. We have been able to preserve a rabid encephalon with its virulence intact for three weeks, at a temperature neighbouring upon 12° C. (50° F.).

6. In order to develop rabies rapidly and with certainty, it is necessary, after trephining, to have recourse to inoculation on the surface of the brain, in the arachnoid space. It is similarly possible both to considerably shorten the period of incubation and to give rise to the disease with certainty, by inoculating the pure virus into the blood stream directly.

M. Roux's co-operation for the application of those methods proved to be both active and valuable. He has acquired such skill in it that accidents after the operations have come to be exceptionally rare.

By having recourse to those methods, which are so favourable to the experimental study of the disease, rabies now declares itself at the end of the sixth, eighth, or tenth day.

7. Rabies communicated by intravenous injection of the virus very often exhibits characters which differ considerably from those of furious rabies

supervening upon a bite or after trephining, and it is likely that many cases of silent madness have passed unobserved. In such cases of rabies, which could be termed *spinal*, early paralysis is a common symptom, whilst the habitual fury and rabid barks are absent or rare; but, on the other hand, frightful itching of the skin is at times a marked phenomenon.

The details of our experiments would tend to show that after inoculation of the poison into the blood system, in the way we have indicated, the spinal marrow is the region first attacked, the virus locating itself and multiplying there before spreading to other parts.

8. Inoculation not followed by death, of the saliva or blood of a rabid animal into the veins of a dog, does not subsequently preserve the latter against the development of fatal rabies after a new inoculation of the pure virus made either on the brain after trephining or into a vein. (*These results are in opposition with those announced to this Academy by M. Galtier on August* 1, 1881. *His experiments had been made on sheep.*)

9. We have met with cases of spontaneous cure after the first symptoms of rabies had alone appeared, but never after the advent of the acute symptoms.

We have also met with similar cases in which, after an apparent cure, the disease broke out anew, with acute symptoms followed by death, as in ordinary cases.

10. In one of our experiments three dogs were inoculated, in 1881. Two of them rapidly took the disease and died. The third one exhibited the first symptoms only, and then recovered.

This third dog, inoculated afresh, on the brain, and on two different occasions, in 1882, could not be made to take rabies, so that the disease, although mild in its symptoms, did not occur a second time. This observation constitutes a first step towards the discovery of the prophylaxis of rabies.

11. We at the present time have in our possession four dogs which are not susceptible of taking rabies, whatever method of inoculation be used and whatever also the virulence of the rabid material employed.

All control dogs, inoculated at the same time, took the disease and died.

Those four dogs comprise the one mentioned in paragraph 10. Are the others, like that one, refractory to the disease owing to a previous slight unnoticed attack, from which they recovered, or are they so by nature, if so it be that there are dogs

naturally refractory to rabies? We shall investigate the hypothesis on an early occasion.

One last remark. Man never contracts hydrophobia except after the bite of some rabid animal; in order, then, to preserve him against that terrible disease it will be enough to find out some way of preserving dogs. That result is remote still, but may we not be permitted, in the sight of the facts above referred to, to hope that it is not beyond the reach of modern science?

It was through the kindness of M. Bourel, veterinary surgeon in Paris, and a gentleman well known for his writings on hydrophobia, that we obtained the two first dogs which served for our first experiments, one with furious madness, the other with dumb madness (December 1880). Since that time the disease has been kept up uninterruptedly in my laboratory. On several occasions we have been enabled to make use of dogs that had died of rabies at the Veterinary College at Alfort, owing to the zeal in helping us of Messrs. Goubeaux, the manager, and Nocard, the learned professor of that school. Quite recently, too, M. Rossignol, a veterinary surgeon in Melun, forwarded to us the head of a cow that had died of rabies after the bite of a mad dog.

It is interesting to learn that already all the animals (the last one only this morning) inoculated with the nervous matter of that cow's head, on November 22 last, have now died of rabies. Inoculation was performed after trephining, and the parts used were the following: the medulla oblongata, the middle lobe of the cerebellum, the right sphenoidal lobe, the left frontal lobe. It is evident, therefore, that all the parts of the encephalon of the cow had proved to be favourable media for the cultivation of the virus. And yet all these parts appeared to be perfectly healthy, except the left frontal lobe, which was intensely congested, and the medulla, which was but slightly so.

The preceding propositions are the result of inoculation-experiments on rabies numbering more than two hundred, and carried out on dogs, rabbits, and sheep.

IV. *February* 25, 1884. — The Academy received with favour our preceding communications on rabies, incomplete though they were, justly considering that each step forward in the experimental study of that disease deserved to be encouraged.

The new facts which I shall have the honour to communicate to-day—in my own name and in the

name of my fellow-workers, amongst whom I ought to name Thuillier, who worked with us before he left for Egypt[1]—have all been ascertained by the use of the two highly valuable methods of inoculation of the virus of rabies on the surface of the brain after trephining, and of injection of the same into the blood system. The expression 'after trephining' carries with it the notion of an operation both long and unsafe in itself, and yet it is not so in reality. We have performed it many hundred times on dogs, rabbits, guinea-pigs, fowl, monkeys, sheep and other animals, and yet the failures could easily be counted on the fingers. The manual dexterity required for its application is also within the reach of most people. A young laboratory assistant was thus very rapidly taught by M. Roux, and is now entrusted with the performance of all our trephining operations, and the operative casualties are altogether unimportant. Neither is the operation lengthy. The last monkey trephined was chloroformed, operated upon, and got over the after-effects of the anæsthetic in twenty minutes. In another quarter of an hour he

[1] Louis Thuillier went out to Egypt, where an epidemic of cholera was raging. His object was to study the disease from a bacteriological point of view. He took the infection and died.—AUTHOR.

was eating a fig. In order to make this paper shorter I shall content myself with giving, in the form of conclusions, the sum of the results come to.

1. In the communication of December 11, 1882, I said that the inoculation of the virus of rabies into the blood system generally gave rise to paralytic rabies, with absence of furor and rabid voice. It seemed probable in those conditions that the virus fixed itself and multiplied, first of all, in the spinal cord. We sacrificed several dogs on the appearance of the first symptoms of paralysis, and then, by a comparative study of the spinal cord (in the lumbar swelling in particular) and of the medulla oblongata, we discovered that the former was occasionally virulent when the latter was not yet so.

2. It has been shown already that the virus of rabies is located in the encephalon and in the spinal cord. We have more recently looked for it in the nerves themselves, and in the salivary glands. We have been able to reproduce the disease by means of small portions of the pneumogastric taken either near its origin, just outside the cranium, or at more distant points. So also with the sciatic nerves, and the submaxillary,

parotid, and sublingual glands. The whole nervous system, then, from the centre to the periphery, is capable of cultivating the virus. It is thus easy to explain the nervous excitement which is so often present in rabies, and which in man gives rise to the strange symptom known as aërophobia.

The saliva and salivary glands have been found virulent in dogs made mad by intra-cranial inoculations, by intra-venous inoculations, and in those affected with the so-called spontaneous disease.

3. We had previously ascertained that the rabies virus could retain its virulence intact for several weeks in the encephalon and cord, if the cadavers were preserved from putrefaction by keeping them at a temperature ranging from 0° to 12° C. (32° F. to 53°·60 F.)

We have now found that the virus enclosed pure in glass tubes sealed with the blow-pipe could also be preserved for three weeks or one month, even at summer heat.

4. We have, again, ascertained that the rabies virus is occasionally present in the cerebro-spinal fluid, but not constantly so. In some cases that fluid, when perfectly limpid, gave rise to rabies, whilst in other cases, although perceptibly turbid and opalescent, it remained quite inert.

5. We have made many attempts to obtain 'cultures'—crops—of the virus of rabies in this same cerebro-spinal fluid, in various other substances, and even in the spinal cord taken out pure from animals killed whilst in a state of perfect health. We have not hitherto been successful. 'Possibly there is no such thing as a microbe of rabies?' inquired last May our colleague, M. Bouley. 'All I can say,' answered I, 'is this, that if you were to bring me two brains, the one rabid and the other healthy, I could say from a microscopic examination of the two medullas, this one is rabid, that one is not. Both show an immense number of molecular granules, but those in the rabid medulla are finer, more numerous, suggesting the idea of a micro-organism of extreme tenuity, in shape neither a bacillus nor a diplococcus; they are like simple dots.'

One method alone, hitherto, has allowed us to isolate those granules from all the other elements of the nervous matter. It consists in injecting the pure virus taken from the medulla of an animal which had died from hydrophobia into the veins of a rabid animal just at the time when asphyxia is coming on. In a very few hours the blood of the animal is found to contain exclusively the infinitely

small granules we are speaking of, the normal elements of the nervous matter having either been stopped in the capillaries or having, more probably, been digested in the blood. It has also become easy, under these new conditions, to stain them with the aniline dyes.[1]

With regard to the blood of rabid animals, we have in one instance been able to give hydrophobia to a dog by means of the blood of a rabbit which had died of that disease. We shall have occasion to refer again to this important case.

One point in particular occupied our attention.

It is well known that the bitten dog, if he take the disease at all, shows in the majority of cases symptoms of furious rabies with a propensity to bite and the special 'rabid voice' (*aboiement rabique*). In the habitual run of our experiments, when we inoculate the rabies virus into a vein or into the subcutaneous areolar tissue, we more often give rise to the dumb or paralytic form of madness, voiceless and tame. By intra-cranial inoculation, on the other hand, the rule is that furious madness is produced. We have also ascertained that it is possible to give rise to furious madness by intra-

[1] We are not yet absolutely certain that these granulations are actually the germs of rabies, but are busy collecting proof.

venous or subcutaneous inoculation, provided that very small quantities only of the virus be used. The smaller the quantity of virus, or disease material, used in the intra-venous or hypodermic inoculation, the more certainly is the furious form of rabies reproduced.

We have found, on the other hand, that by inoculating small quantities of virus the duration of incubation was considerably increased; and the same virus, if diluted beyond a certain limit, which is not very far, remains without effect when inoculated. The considerable interest attaching to those conclusions justifies me in giving the details of two experiments.

On May 6, 1883, we inoculate into the vein of the right popliteal space (behind the knee) of three dogs portions of a rabid medulla diluted in sterilised broth. To the first dog we give half a cubic centimetre of the turbid liquid, to the second one-hundredth part of that quantity, to the third the two-hundredth part only.

As early as the tenth day, the first dog begins to lose his appetite, and on the eighteenth day he is completely paralysed; he dies two days later without having at any time had the peculiar bark of mad dogs, or tried to bite. On the thirty-seventh day after inoculation the second dog still eats well; on the thirty-eighth day he begins to look suspicious; on the thirty-ninth day he has the rabid voice, and is found dead the next day. The third dog has not taken the disease at all.

Another experiment consisted in inoculating into a popliteal vein one cubic centimetre of rabid matter in sterilised broth for the first dog, one-twentieth of that quantity for a second dog, one-fiftieth for a third dog. The incubative periods were respectively seven, twenty, and twenty-five days. The two first dogs took paralytic madness, the third had the furious, barking and biting form.

Whenever the small quantities injected failed to give rise to rabies, we ascertained that the animals were liable to take the disease by new and subsequent inoculations.

In other words, the inoculation of small quantities of the virus failed to produce immunity.

6. In my last paper on rabies I said that we had met with some dogs in whom the first symptoms of the disease subsided and disappeared, to reappear again after a tolerably long period of latency. We have since then met with similar cases in the rabbit. To quote one instance: on the thirteenth day after intra-cranial inoculation, one of our rabbits showed the first symptoms of paralysis. On the following days he got better and recovered completely, but forty-three days later the paralysis returned and he died of paralytic rabies on the forty-sixth day.

7. Such cases are very rare in the rabbit as well

as in the dog, but we have very frequently noticed them in hens, in which latter animals the recurrence of the symptoms may or may not be followed by death. We have already, in our last note, mentioned a case of such recurrence of rabies in the dog, not followed by death. I may just note here that rabies in our hens never showed any violent symptoms, but only a degree of sleepiness, loss of appetite, paralysis of the legs, and frequently a considerable degree of anæmia or bloodlessness, as shown by the blanching of the comb.

8. We were particularly careful in our control experiments as to certain recent assertions concerning the alleged attenuation of the rabies virus by the action of cold, and also as to the asserted passage of rabies from the mother to the unborn young.

Although our experiments bearing on both of those points have been much more numerous than those which were brought forward in support of them, our results have constantly been negative.

9. The certainty of inoculation by intra-venous injection of the virus is in itself sufficient proof that the nerves are not the sole channels of propagation of the virus from the periphery or surface to the centre, as one theory would have it, and proof

enough also, that in the majority of cases, to say the least, the absorption of the virus is effected through the blood-system.

And yet, after all, this view of the case is still open to discussion. In order to inject the virus into a vein we must still make a wound, cut the skin and bare the vessel. Might it not be then that the virus, introduced at first into the blood circulation, was at once brought back by it to the seat of the wound, in contact with the nerve fibres and the lymphatic vessels which have been inevitably cut, and are all ready to absorb it? The following experiment does away completely with that objection. We have on several different occasions inoculated the virus into one of the veins of the ear, and then, immediately after, cut off that organ with the thermo-cautery between the point of inoculation and the head. Nevertheless, rabies showed itself in every instance, although, as all know, the thermo-cautery does not produce an open wound, the whole of the cut surface being burnt.

But I must hasten to speak of the point of greatest interest. The discovery of the attenuation of different viruses and the application of it to the prophylaxis or prevention of several diseases have thrown full light upon the capital fact of the

possible production, experimentally, of different states in the virulence of the same virus.

Rabies is above all others a virulent disease. The mode of action and the nature of its virus are surrounded with so much mystery that it becomes very natural for one to investigate whether rabies virus is also capable of exhibiting varying degrees in its virulence. Experimentation has taught us that the answer must be in the affirmative. Whilst waiting for the proof afforded by other methods which are still in course of study, we have already ascertained that a given rabies virus has its virulence modified, more or less deeply, by passing it through different species of animals. Rabbits, guinea-pigs, hens, monkeys, are all susceptible of taking rabies. By a succession of passages through animals of the same race the virus after a time reaches, so to speak, a fixed degree of virulence for that race, the degree being different for different races of animals and always perceptibly different from the fixed virulence of ordinary canine madness, which has itself come to its present degree of fixity after countless transfers by bites throughout the past ages. In my idea there is no such thing as spontaneous rabies.

We are in possession at the present time of a

virus which produces rabies in the rabbit in seven or eight days, and with such constancy that we can, within a few hours, foretell the duration of incubation as measured from the time of inoculation to the first appearance of a change in the temperature of the animal or of the first external symptoms of the disease.

We have also a virus which gives rabies to guinea-pigs in five or six days, with no less certainty as to the duration of the incubative period.

Before it reaches the degree of fixity of which we are speaking in the different animal species, the virulence passes through a series of incessant variations. We count that the virulence is in the inverse ratio of the number of days' incubation when other circumstances remain the same, and when, in particular, the quantity of virus inoculated remains as much as possible the same for the same mode of inoculation. The incubative period is in general slightly shorter in young animals than in the full-grown ones.

Seeing that we know absolutely nothing regarding the new conditions which the rabies virus of the dog would assume by successive passages from man to man, we were led to try a succession of passages from monkey to monkey.

I shall later on communicate the very interesting results of those experiments, as they are not yet completed.

I have already said that I have in my laboratory several dogs which are refractory to rabies, in whatever way inoculated to them. I am in a position to add to-day that they are also refractory to all sorts or degrees of rabies viruses. Nevertheless, we had been obliged at the time of my last communication to the Academy, owing to the incompleteness of our observations at that moment, to ask ourselves whether those dogs were by nature refractory to rabies, or whether they had become so by reason of the operations which they had anteriorly undergone.

We are able to-day to answer those questions with more precision, although our answers must still be somewhat guarded.

I believe I am authorised to assert that our dogs were not by natural disposition refractory to rabies. We have, as a matter of fact, discovered a method of rendering dogs refractory to rabies in numbers as large as it may be desired. However, if we consider that the length of incubation of rabies is uncertain, and in some cases very protracted, there must always linger some little doubt as to the

thoroughness of the proof afforded by control experiments, and I must needs beg of the Academy to give credit to this assertion yet for a little time, and to allow me, further, to restrict myself for the present to this statement, that the refractory state is obtained by a series of inoculations of viruses of different degrees. We possess at the present moment twenty-three dogs capable of bearing without danger the most virulent inoculations.

By rendering dogs refractory to rabies we solve the question of the prophylaxis of that affection not only in the dog but also in man, seeing that man never takes rabies except after a bite the virus of which comes directly or indirectly from the dog.

Lengthy is the incubation of rabies: will not human medicine be able, some day, taking advantage of that respite time, to render the bitten victim refractory before the first symptoms of the malady break out? Before that hope becomes a reality we have yet a long and weary way to travel.

V. *May* 19, 1884.—*The Attenuation of Rabies.*—The great notions of the variability in the virulence of certain viruses, and of the preservation against a given virus by the inoculation of another of lower intensity, are to-day recognised scientific facts already put to practical uses. It is easy to appre-

hend all the interest attaching, in that line of study, to the search after methods of attenuation applicable to new viruses.

I bring news to-day of one more step forward in that direction as concerns rabies.

1. The virus of rabies carried from the dog to the monkey, and subsequently from monkey to monkey, grows weaker at each passage. After the virulence has thus diminished by several passages through monkeys, if the virus be carried back to the dog or to the rabbit or to the guinea-pig, it still remains attenuated. In other words, the virulence does not at one bound go back to the degree it had in the dog 'a rage des rues'—affected with ordinary or street madness.

In those conditions a small number of passages from monkey to monkey suffice to bring down the attenuation to a point at which the virus injected hypodermically into dogs never gives rise to rabies in them. Intra-cranial inoculation itself, the never-failing means of communicating rabies, may now remain without effect, whilst, however, creating a refractory state in favour of the inoculated animal.

2. Successive passages from rabbit to rabbit and from guinea-pig to guinea-pig increase the virulence of rabies virus. This exalted virulence

comes to a fixed maximum in the rabbit. If now transferred to the dog it remains exalted, and shows itself to be much more intensely virulent than the virus of ordinary street rabies. So great is this acquired virulence, that the new virus injected into the blood-system of a dog unfailingly gives rise to mortal madness.

3. The virulence of rabies virus, as we have seen, is exalted by its passages through rabbits or through guinea-pigs, but it requires many such passages before it again reaches its maximum degree after it has been weakened in the monkey. In the same way the virus of ordinary canine madness, as I have just said, is far from possessing the maximum degree of virulence, and it requires several passages through rabbits before it reaches that maximum.

A logical application of the results just indicated gives us the means of easily rendering dogs refractory to rabies, for we can now prepare and keep at our disposal a set of attenuated viruses of different strength, some, not mortal, preserving the animal economy against the ill effects of more active ones, and these latter against the effects of mortal ones.

Let us give an example: take a rabbit which has been inoculated on the brain, and which has died of rabies after a period of incubation longer by

several days than the shortest known incubation in the rabbit (this is always comprised between seven and eight days after intra-cranial inoculation of the maximum virus). Extract the virus from this long-incubation rabbit and inject it, after trephining, into a second rabbit. Similarly inoculate a third rabbit from this second one. These viruses have grown stronger each time; each time also that they are inoculated into a fresh rabbit, let us inoculate them into the same dog. This dog, after the third inoculation, has become capable of bearing unhurt inoculations of a mortal virus. He has become entirely refractory to the rabies of ordinary canine madness, whether inoculated into a vein or into the arachnoid space.

By inoculating the blood of rabid animals, under certain well-determined circumstances, I have been able considerably to simplify the process of vaccination, whilst at the same time putting the dog in a most decidedly refractory state. I shall on an early occasion acquaint the Academy with the sum of my experiments on that point.

In the meantime, and until we come to that remote epoch when vaccination shall have stamped out rabies from our midst, it would be highly advantageous to have the means of preventing the

development of that affection after the bite of mad dogs. The first attempts I have made in that direction inspire me with the greatest hopes of success. Owing to the long incubative period of rabies I have every reason to believe that we shall be able with certainty, after the bite, to put the patients in a refractory state before the first symptoms of the mortal malady show themselves.

The first experiments testify strongly in favour of this view, but afferent proof must be collected from different animal races, and almost *ad infinitum*, before human therapeutics can make bold enough to try this mode of prophylaxis on man himself.

Notwithstanding the confidence I derive from the large number of the experiments I have made in the last four years, it is not without some excusable apprehension that I publish to-day a set of facts which point to no less a result than the possible prophylaxis of rabies. Had I been able to dispose of the necessary materials I should have been glad before giving this communication to wait until I had begged of some of my colleagues of the Academy of Sciences and of the Academy of Medicine kindly to witness and to control the conclusions I have just brought forward.

In order to obey those scruples and those reasons I took the liberty of writing a few days ago to M. Fallières, Minister of Public Instruction, requesting of him to appoint a commission before which I might bring my rabies-refractory dogs.

The crucial experiment to be tried in the first instance would be the following. I should take from my kennels twenty refractory dogs, which I should place, for the sake of comparison, by the side of twenty ordinary, non-vaccinated control dogs. We should then have the forty dogs brought in with mad dogs and bitten by them. If the facts announced by me are real, not one of my twenty dogs will take rabies, whereas the twenty control animals will take it.

A second experiment, no less conclusive than the first, would consist in taking forty dogs, whereof twenty should be vaccinated before the eyes of the commission and twenty should remain not vaccinated. The forty animals will then be trepanned and inoculated on the brain with the virus of ordinary street-dog rabies. The twenty vaccinated dogs will not take rabies but the twenty others will all die of it, taking it either in its paralytic or in its furious form.

The following communication was made to the

members of the International Medical Congress sitting in Copenhagen, on August 11, 1884. *Although not a communication to the Académie des Sciences, we give it here in full, because of its intrinsic interest and importance, and also because it forms an otherwise missing link between some of the other articles:*

'Gentlemen,—Your Congress meetings are the place for the discussion of the gravest problems of medicine; they serve also to point out the great landmarks of the future. Three years ago, on the eve of the London Congress, the doctrine of micro-organisms, the ætiological cause of transmissible maladies, was still the subject of sharp criticisms. Certain refractory minds continued to uphold the idea that "disease is in us, from us, by us."

'It was expected that the decided supporters of the theory of the spontaneity of diseases would make a bold stand in London; but no opposition was made to the doctrine of "exteriority," or external causes, the first cause of contagious diseases, and those questions were not discussed at all.

'It was there seen, once again, that when all is ready for the final triumph of truth, the united conscience of a great assembly feels it instinctively and recognises it.

'All clear-sighted minds had already foreseen that

the theory of the spontaneity of diseases received its death-blow on the day when it became possible reasonably to consider the spontaneous generation of microscopic organisms as a myth, and when, on the other hand, the life-activity of those same beings was shown to be the main cause of organic decomposition and of all fermentation.

'From the London Congress, also, dates the recognition of another very hopeful progress, we refer to the attenuation of different viruses, to the production of varying degrees of virulence for each virus, and their preservation by suitable methods of cultivation; to the practical application, finally, of those new facts in animal medicine.

'New microbic prophylactic viruses have been added to those of fowl-cholera and of splenic fever. The animals saved from death by contagious diseases are now counted by hundreds of thousands, and the sharp opposition which those scientific novelties met with at the beginning was soon swept away by the rapidity of their onward progress.

'Will the circle of practical applications of those new notions be limited in future to the prophylaxis of animal distempers? We must never think little of a new discovery, nor despair of its fecundity; but more than that, in the present instance, it may

be asserted that the question is already solved in principle. Thus, splenic fever is common to animals and man, and we make bold to declare that, were it necessary to do so, nothing could be easier than to render man also proof against that affection. The process which is employed for animals might, almost without a change, be applied to him also. It would simply become advisable to act with an amount of prudence which the value of the life of an ox or a sheep does not call for. Thus, we should use three or four vaccine-viruses instead of two, of progressive intensity of virulence, and choose the first ones so weak that the patient should never be exposed to the slightest morbid complication, however susceptible to the disease he might be by his constitution.

'The difficulty, then, in the case of human diseases, does not lie in the application of the new method of prophylaxis, but rather in the knowledge of the physiological properties of their viruses. All our experiments must tend to discover the proper degree of attenuation for each virus. But experimentation, if allowable on animals, is criminal on man. Such is the principal cause of the complication of researches bearing on diseases exclusively human. Let us keep in mind, nevertheless, that

the studies of which we are speaking were born yesterday only, that they have already yielded valuable results, and that new ones may be fairly expected when we shall have gone deeper into the knowledge of animal maladies, and of those in particular which affect animals in common with man.

'The desire to penetrate farther forward in that double study led me to choose rabies as the subject of my researches, in spite of the darkness in which it was veiled.

'The study of rabies was begun in my laboratory four years ago, and pursued since then without other interruption than what was inherent to the nature of the researches themselves, which present certain unfavourable conditions. The incubation of the disease is always protracted, the space disposed of is never sufficient, and it thus becomes impossible at a given moment to multiply the experiments as one would like. Notwithstanding those material obstacles, lessened by the interest taken by the French Government in all questions of great scientific interest, we now no longer count the experiments which we have made, my fellow-workers and myself. I shall limit myself to-day to an exposition of our latest acquisitions.

'The name alone of a disease, and of rabies above all others, at once suggests to the mind the notion of a remedy.

'But it will, in the majority of cases, be labour lost to aim in the first instance at discovering a mode of cure. It is, in a manner, leaving all progress to chance. Far better to endeavour to acquaint oneself, first of all, with the nature, the cause, and the evolution of the disease, with a glimmering hope, perhaps, of finally arriving at its prophylaxis.

'To this last method we are indebted for the result that rabies is no longer to-day to be considered as an insoluble riddle.

'We have found that the virus of rabies develops itself invariably in the nervous system, brain, and spinal cord, in the nerves, and in the salivary glands; but it is not present at the same moment in every one of those parts. It may, for example, develop itself at the lower extremity of the spinal cord, and only after a time reach the brain. It may be met with at one or at several points of the encephalon whilst being absent at certain other points of the same region.

'If an animal is killed whilst in the power of rabies, it may require a pretty long search to dis-

cover the presence here or there in the nervous system, or in the glands, of the virus of rabies. We have been fortunate enough to ascertain that in all cases, when death has been allowed to supervene naturally, the swelled-out portion, or bulb, of the medulla oblongata nearest to the brain, and uniting the spinal cord with it, is always rabid. When an animal has died of rabies (and the disease always ends in death), rabid matter can with certainty be obtained from its bulb, capable of reproducing the disease in other animals when inoculated into them, after trephining, in the arachnoid space of the cerebral meninges.

'Any street dog whatsoever, inoculated in the manner described with portions of the bulb of an animal which has died of rabies, will certainly develop the same disease. We have thus inoculated several hundreds of dogs brought without any choice from the pound. Never once was the inoculation a failure. Similarly also, with uniform success, several hundred guinea-pigs, and rabbits more numerous still.

'Those two great results, the constant presence of the virus in the bulb at the time of death, and the certainty of the reproduction of the disease by inoculation into the arachnoid space, stand out

like experimental axioms, and their importance is paramount. Thanks to the precision of their application, and to the well-nigh daily repetition of those two criteria of our experiments, we have been able to move forward steadily and surely in that arduous study. But, however solid those experimental bases, they were, nevertheless, incapable in themselves of giving us the faintest notion as to some method of vaccination against rabies. In the present state of science the discovery of a method of vaccination against some virulent malady presupposes :

'1. That we have to deal with a virus capable of assuming diverse intensities, of which the weaker ones can be put to vaccinal or protective uses.

'2. That we are in possession of a method enabling us to reproduce those diverse degrees of virulence at will.

'At the present time, however, science is acquainted with one sort of rabies only—viz., dog rabies.

'Rabies, whether in dog, man, horse, ox, wolf, fox, &c., comes originally from the bite of a mad dog. It is never spontaneous, neither in the dog nor in any other animal. There are none seriously authenticated among the alleged cases of so-called

spontaneous rabies, and I add that it is idle to argue that the first case of rabies of all must have been spontaneous. Such an argument does not solve the difficulty, and wantonly calls into question the as yet inscrutable problem of the origin of life. It would be quite as well, against the assertion that an oak-tree always proceeded from another oak-tree, to argue that the first of all oak-trees that ever grew must have been produced spontaneously. Science, which knows itself, is well aware that it would be useless for her to discuss about the origin of things; she is aware that, for the present at any rate, that origin is placed beyond the ken of her investigations.

'In fine, then, the first question to be solved on our way towards the prophylaxis of rabies is that of knowing whether the virus of that malady is susceptible of taking on varying intensities, after the manner of the virus of fowl-cholera or of splenic fever.

'But in what way shall we ascertain the possible existence of varying intensities in the virus of rabies? By what standard shall we measure the strength of a virus which either fails completely or kills? Shall we have recourse to the visible symptoms of rabies? But those symptoms are

extremely variable, and depend essentially on the particular point of the encephalon or of the spinal cord where the virus has in the first instance fixed and developed itself. The most caressing rabies, for such do exist, may, when inoculated into another animal of the same species, give rise to furious rabies of the intensest type.

'Might we then perhaps make use of the duration of incubation as a means of estimating the intensity of our virus? But what can be more changeful than the incubative period? Suppose a mad dog to bite several sound dogs: one of them will take rabies in one month or six weeks, another after two or three months or more. Nothing, too, more changeful than the length of incubation according to the different modes of inoculation. Thus, other circumstances the same, after bites or hypodermic inoculation rabies occasionally develops itself, and at other times aborts completely: but inoculations on the brain are never sterile, and give the disease after a relatively short incubation.

'It is possible, nevertheless, to gauge with sufficient accuracy the degree of intensity of our virus by means of the time of incubation, on condition that we make use exclusively of the intra-cranial mode of inoculation; and secondly, that we do away

with one of the great disturbing influences inherent to the results of inoculation made by bites, under the skin, or in the veins, by injecting the right proportion of material.

'The duration of incubation, as a matter of fact, may depend largely on the quantity of efficient virus—that is to say, on the quantity of virus which reaches the nervous system without diminution or modification. Although the quantity of virus capable of giving rabies may be, so to speak, infinitely small, as seen in the common fact of the disease developing itself after rabid bites which, as a rule, introduce into the system a barely appreciable weight of virus, it is easy to double the length of incubation by simply changing the proportion of those very small quantities of inoculated matter. I may quote the following examples :—

'On May 10, 1882, we injected into the popliteal vein of a dog ten drops of a liquid prepared by crushing a portion of the bulb of a dog, which had died of ordinary canine madness, in three or four times its volume of sterilised broth.

'Into a second dog we injected $\frac{1}{100}$th of that quantity, into a third $\frac{1}{200}$th. Rabies showed itself in the first dog on the eighteenth day after the injection, on the thirty-fifth day in the second dog,

whilst the third one did not take the disease at all, which means that, for that last animal, with the particular mode of inoculation employed, the quantity of virus injected was not sufficient to give rabies. And yet that dog, like all dogs, was susceptible of taking the disease, for it actually took it twenty-two days after a second inoculation, performed on September 3, 1882.

'I now take another example bearing on rabbits, and by a different mode of inoculation. This time, after trephining, the bulb of a rabbit which had died of rabies after inoculation of an extremely powerful virus is triturated and mixed with two or three times its volume of sterilised broth. The mixture is allowed to stand a little, and then two drops of the supernatant liquid are injected after trephining into a first rabbit, into a second rabbit one-fourth of that quantity, and in succession into other rabbits, $\frac{1}{15}$th, $\frac{1}{64}$th, $\frac{1}{128}$th, and $\frac{1}{512}$nd of that same quantity. All those rabbits died of rabies, the incubation having been eight days, nine and ten days for the third and fourth, twelve and sixteen days for the last ones.

'Those variations in the length of incubation were not the result of any weakening or diminution of the intrinsic virulence of the virus brought on

possibly by its dilution, for the incubation of eight days was at once recovered when the nervous matter of all those rabbits was inoculated into new animals.

'Those examples show that, whenever rabies follows upon bites or hypodermic inoculations, the differences in respect of length of incubation must be chiefly ascribed to the variations, at times within considerable limits, of the ever-undeterminate proportions of the inoculated viruses which reach the central nervous system.

'If, therefore, we desire to make use of the length of incubation as a measure of the intensity of the virulence, it will be indispensable to have recourse to inoculation on the surface of the brain, after trephining, a process the action of which is absolutely certain, coupled with the use of a larger quantity of virus than what is strictly sufficient to give rise to rabies. By those means the irregularities in the length of incubation for the same virus tend to disappear completely, because we always have the maximum effect which that virus can produce; that maximum coincides with a minimum length of incubation.

'We have thus, finally, become possessed of a method enabling us to investigate the possible exist-

ence of different degrees of virulence, and to compare them with one another. The whole secret of the method, I repeat, consists in inoculating on the brain, after trephining, a quantity of virus which, although small in itself, is still greater than what is simply necessary to reproduce rabies. We thus disengage the incubation from all disturbing influences and render its duration dependent exclusively on the activity of the particular virus used, that activity being in each case estimated by the minimum incubation determined by it.

'This method was applied in the first instance to the study of canine madness, and in particular to the question of knowing whether dog-madness was always one and the same, with perhaps the slight variations which might be due to the differences of race in diverse dogs.

'We accordingly got hold of a number of dogs affected with ordinary street rabies, at all times of the year, at all seasons of the same year or of different years, and belonging to the most dissimilar canine races. In each case the bulbar portion of the medulla oblongata was taken out from the recently dead animal, triturated and suspended in two or three times its volume of sterilised liquid, making use all along of every precaution to keep our mate-

rials pure, and two drops of this liquid injected after trephining into one or two rabbits. The inoculation is made with a Pravaz syringe, the needle of which, slightly curved at its extremity, is inserted through the dura-mater into the arachnoid space. The results were as follows: all the rabbits, from whatever sort of dog inoculated, showed a period of incubation which ranged between twelve and fifteen days, without almost a single exception. Never did they show an incubation of eleven, ten, nine, or eight days, never an incubation of several weeks or of several months.

'Dog-rabies, the ordinary rabies, the only known rabies, is thus sensibly one in its virulence, and its modifications, which are very limited, appear to depend solely on the varying aptitude for rabies o the different known races. But we are going now to witness a deep change in the virulence of dog-rabies.

'Let us take one, any one, of our numerous rabbits, inoculated with the virus of an ordinary mad dog, and, after it has died, extract its bulb, prepare it as just described, and inject two drops of the bulb-emulsion into the arachnoid space of a second rabbit whose bulb will in turn and in time be injected into a third rabbit, the bulb of

which again will serve for a fourth rabbit, and so on.

'There will be evidence, even from the first few passages, of a marked tendency towards a lessening of the period of incubation in the succeeding rabbits. Just one example:

'Towards the end of the year 1882, fifteen cows and one bull died of rabies in a farm situated in the neighbourhood of the town of Melun. They had been bitten on October 2 by the farm-dog, which had become mad. The head of one of the cows, which had died on November 15, was sent to my laboratory by M. Rossignol, a veterinary surgeon in Melun. A number of experiments were made on dogs and on rabbits, and showed that the following parts, the only encephalic (or those pertaining to the brain) ones tested, were rabid: the bulb, the cerebellum, the frontal lobe, the sphenoidal lobe. The rabbits trephined and inoculated with those different parts showed the first symptoms of rabies on the seventeenth and the eighteenth days after inoculation. With the bulb of one of those rabbits two more were inoculated, of which one took rabies on the fifteenth day, the other on the twenty-third day.

'We may notice, once for all, that when rabies is transferred from one animal to another of a

different species, the period of incubation is always very irregular at first in the individuals of the second species if the virus had not yet become fixed in its maximum virulence for the first species. We have just seen an example of that phenomenon, since one of the rabbits had an incubation of fifteen days, the other of twenty-three days, both having received the same virus and all other circumstances remaining apparently the same for them.

The bulb of the first one of those last rabbits which died was injected into two more rabbits, still after trephining. One of them took rabies on the tenth day, the other on the fourteenth day. The bulb of the first one that died was again injected into a couple of new rabbits, which developed the disease in ten days and twelve days respectively. A fifth time two new animals were inoculated from the first one that died, and they both took the disease on the eleventh day after inoculation; similarly, a sixth passage was made, and gave an incubation of eleven days, twelve days for the seventh passage, ten and eleven for the eighth, ten days for the ninth and tenth passages, nine days for the eleventh, eight and nine days for the twelfth, and so on, with differences of twenty-four hours at the most, until we got to the twenty-first passage, when rabies de-

clared itself in eight days, and subsequently to that always in eight days up to the fiftieth passage, which was only effected a few days ago. That long experimental series which is still going on was begun on November 15, 1882, and will be kept up for the purpose of preserving in our rabies virus that maximum virulence which it has come to now for some considerable time, as it is easy to calculate.

'Allow me to call your attention to the ease and safety of the operations for trephining and then inoculating the virus. Throughout the last twenty months we have been able without a single interruption in the course of the series to carry the one initial virus through a succession of rabbits which were all trephined and inoculated every twelfth day or so.

'Guinea-pigs reach more rapidly the maximum virulence of which they are susceptible. The period of incubation is in them also variable and irregular at the beginning of the series of successive passages, but it soon enough fixes itself at a minimum of five days. The maximum virulence in guinea-pigs is reached after seven or eight passages only. It is worth noting that the number of passages required before reaching the maximum virulence, both in

guinea-pigs and in rabbits, varies with the origin of the first virus with which the series is begun.

'If now this rabies with maximum virulence be transferred again into the dog from guinea-pig or rabbit, there is produced a dog-virus which in point of virulence goes far beyond that of ordinary canine madness.

'But, a natural query—of what use can be that discovery as to the existence and artificial production of diverse varieties of rabies, every one of them more violent and more rapidly fatal than the habitual madness of the dog? The man of science is thankful for the smallest find he can make in the field of pure science, but the many, terrified at the very name of hydrophobia, claim something more than mere scientific curiosities. How much more interesting it would be to become acquainted with a set of rabies viruses which should, on the contrary, be possessed of attenuated degrees of virulence! Then, indeed, might there be some hope of creating a number of vaccinal rabies viruses such as we have done for the virus of fowl-cholera, of the microbe of saliva, of the red evil of swine (swine-plague), and even of acute septicæmia. Unfortunately, however, the methods which had served for those different viruses showed themselves to be either inapplicable

or inefficient in the case of rabies. It, therefore, became necessary to find out new and independent methods, such, for example, as the cultivation *in vitro* of the mortal rabies virus.

'Jenner was the first to introduce into current science the opinion that the virus which he called the grease of the horse, and which we call now more exactly horse-pox, probably softened its virulence, so to speak, in passing through the cow and before it could be transferred to man without danger. It was, therefore, natural to think of a possible diminution of the virulence of rabies by a number of passages through the organisms of some animal or other, and the experiment was worth trying. A large number of attempts were made, but the majority of the animal species experimented on exalted the virulence after the manner of rabbits and guinea-pigs; fortunately, however, it was not so with the monkey.

'On December 6, 1883, a monkey was trephined and inoculated with the bulb of a dog, which had itself been similarly inoculated from a child who had died of rabies. The monkey took rabies eleven days later, and when dead served for inoculation into a second monkey which also took the disease on the eleventh day. A third monkey, similarly

inoculated from the second one, showed the first symptoms on the twenty-third day, &c. The bulb of each one of the monkeys was inoculated, after trephining, into two rabbits each time. The rabbits inoculated from the first monkey developed rabies between thirteen and sixteen days, those from the second monkey between fourteen and twenty days, those from the third monkey between twenty-six and thirty days, those from the fourth monkey both of them after the twenty-eighth day, those from the fifth monkey after twenty-seven days, those from the sixth monkey after thirty days.

'It cannot be doubted after that, that successive passages through monkeys, and from the several monkeys to rabbits, do diminish the virulence of the virus for the latter animals; they diminish it for dogs also. The dog inoculated with the bulb of the fifth monkey gave an incubation of no less than fifty-eight days, although it had been inoculated in the arachnoid space.

'The experiments were renewed with fresh sets of monkeys and led to similar results. We were, therefore, actually in possession of a method by means of which we could attenuate the virulence of rabies. Successive inoculations from monkey to monkey elaborate viruses which, when transferred

to rabbits, reproduce rabies in them, but with a progressively lengthening period of incubation. Nevertheless, if one of those rabbits be taken as the first for inoculations through a series of rabbits, the rabies thus cultivated obeys the law which we have seen before, and has its virulence increased at each passage.

'The practical application of those facts gives us a method for the vaccination of dogs against rabies. As a starting-point, make use of one of the rabbits inoculated from a monkey sufficiently removed from the first animal of the monkey series for the inoculation—hypodermic or intra-venous—of that rabbit's bulb not to be mortal for a new rabbit. The next vaccinal inoculations are made with the bulbs of rabbits derived by successive passages from that first rabbit.

'In the course of our experiments we made use, as a rule, for inoculation, of the virus of rabbits which had died after an incubation of four weeks, repeating three or four times each the vaccinal inoculations made with the bulbs of rabbits derived in succession from one another and from the first one of the series, itself coming directly from the monkey. I abstain from giving more details, because certain experiments which are actually going

on allow me to expect that the process will be greatly simplified.

'You must be feeling, gentlemen, that there is a great blank in my communication; I do not speak of the micro-organism of rabies. We have not got it. The process for isolating it is still imperfect, and the difficulties of its cultivation outside the bodies of animals have not yet been got rid of, even by the use, as pabulum, of fresh nervous matter. The methods which we employed in our study of rabies ought all the more perhaps, on that account, to fix attention. Long still will the art of preventing diseases have to grapple with virulent maladies the micro-organic germs of which will escape our investigations. It is, therefore, a capital scientific fact that we should be able, after all, to discover the vaccination process for a virulent disease without yet having at our disposal its special virus and whilst yet ignorant of how to isolate or to cultivate its microbe.

'As soon as the method for the vaccination of dogs was firmly established, and we had in our possession a large number of dogs which had been rendered refractory to rabies, I had the idea of submitting to a competent committee those of the facts which appeared destined in future to serve as

a basis for the vaccination of dogs against rabies. That course was suggested to me, in prevision of the later practical application of the method, by the recollection of the opposition with which Jenner's discovery met at its beginning.

'I spoke of my project to M. Fallieres, the Minister of Public Instruction, who was pleased to approve of it and gave commission to the following gentlemen to control the facts which I had summarily communicated to the Academy of Sciences in its sitting of May 19 last: Messrs. Béclard, Paul Bert, Bouley, Aimeraud, Villemin, Vulpian. M. Bouley was appointed president, Dr. Villemin secretary, and the commission at once set to work. I have the pleasure of informing you that it has just sent in a first report to the Minister. I was acquainted with it here, and the following are in a few words the facts related in that first report on rabies. I had given to the commission nineteen vaccinated dogs in succession—that is to say, dogs which had been rendered refractory by preventive inoculations. Thirteen only of them had after their vaccination been already submitted to the test-inoculation on the brain.

'The nineteen dogs were, for the sake of comparison, divided into sets along with nineteen more

control dogs brought from the pound without any sort of selection. To begin with, two refractory dogs and two control dogs were on June 1 trephined and inoculated under the dura-mater, on the surface of the brain, with the bulb of a dog affected with ordinary street rabies.

'On June 3 another refractory dog and another control dog were bitten by a furious street mad dog.

'The same furious mad dog was on June 4 made to bite still another refractory and another control dog. On June 6 the furious dog which had been utilised on June 3 and 4 died. The bulb was taken out and inoculated, after trephining, into three refractory dogs and three control dogs. On June 10 another street mad dog, having been secured, was, by the commission, made to bite one refractory and one control dog. On June 16 the commission have two new dogs, a refractory one and a control one, bitten by one of the control dogs of June 1, which had been seized with rabies on June 14 in consequence of the inoculation after trephining which it had received on June 1.

'On June 19 the commission get three refractory and three control dogs inoculated before their own eyes in the popliteal vein with the bulb of an

ordinary street mad dog. On June 20 they have inoculated in their presence, and still in a vein, ten dogs altogether, six of them refractory and four just brought from the pound.

'On June 28, the Commission hearing that M. Paul Simon, a veterinary surgeon, had a furious biting mad dog, have four of their dogs, two refractory and two control dogs, taken to his place and bitten by the mad dog.

'The Rabies Commission have, therefore, experimented on thirty-eight dogs altogether—namely, nineteen refractory dogs and nineteen control dogs susceptible of taking the disease. Those of the dogs which have not died in consequence of the operations themselves are still under observation, and will long continue to be. The commission, reporting up to the present moment on their observations as to the state of the animals tried and tested by them, find that out of the nineteen control dogs six were bitten, of which six three have taken rabies. Seven received intra-venous inoculations, of which five have died of rabies. Five were trephined and inoculated on the brain; the five have died of rabies.

'On the other hand, not one of the nineteen vaccinated dogs has taken rabies.

'In the course of the experiments, on July 13, one of the refractory dogs died in consequence of a black diarrhœa which had begun in the first days of July. In order to ascertain whether rabies had anything to do with it as the cause of death, its bulb was at once inoculated, after trephining, into three rabbits and one guinea-pig. All four animals are still to-day in perfect health, a certain proof that the dog died of some common malady, and not of rabies.

'The second report of the Commission will be concerned with the experiments made as to the refractoriness to rabies of twenty dogs to be vaccinated by the Commission themselves.'

(*M. Pasteur then announced that he had just received that same morning the first report addressed to M. Fallières by the Official Commission on Rabies. It states that twenty-three refractory dogs were bitten by ordinary mad dogs, and that not one of them had taken rabies. On the other hand, within two months after the bites, 66 per cent. of the control dogs similarly bitten had already taken the disease.*)

VI. *October* 26, 1885.—*A Method for the Prevention of Rabies after the Bite of a Rabid Animal.*—The prophylaxis of rabies such as I exposed it in my own name and in the name of my fellow-workers in my

preceding notes certainly constituted a real progress in the study of that disease. But the progress realised was more scientific than practical. In application it exposed to various accidents. Not more than fifteen or sixteen dogs in twenty could be made refractory to rabies with certainty.

It was advisable, on the other hand, to end the treatment with a last and very virulent inoculation, a control inoculation, in order both to confirm and to strengthen the refractory state. Furthermore, simple prudence required that one should keep the dogs in sight for a longer period than that of the incubation of the disease as produced by the direct and isolated inoculation of this last virus, so that it was occasionally necessary to wait three or four months before gaining the assurance of having produced a refractory state.

Such serious exigencies would considerably limit the scope of the method in practice.

Finally, it would have been difficult to put the method to emergency uses at a moment's notice, a condition required of it nevertheless, if we consider how casual and unforeseen are the bites of mad animals.

It was necessary, therefore, if possible, to discover a more rapid method, and one capable of

giving, if I may so speak, a state of perfect security in the dog.

And it was impossible, too, before that desideratum was realised, to think of making any trial of the method on man.

After, I might say, innumerable experiments, I have at last found a method of prophylaxis both practical and rapid, and one which has proved successful in the dog with so much constancy in such a considerable number of cases already, that I feel confident of its general applicability to all animals and to man himself.

This new method rests essentially on the following facts: The rabbit, inoculated under the dura-mater, after trephining, with the spinal marrow of an ordinary mad dog, is always affected with rabies; it takes the disease after a length of incubation averaging about fifteen days.

If a second rabbit be inoculated from that first one, a third from the second, and so on, always by the same mode of inoculation, there is soon manifested in the succeeding rabbits a growing tendency towards a shorter incubation.

After a number of passages through rabbits, varying from the twentieth to the twenty-fifth, the incubation falls down to eight days, which remains

the normal incubation time for the next twenty or twenty-five passages. Then it reached an incubation of seven days only, and recurring with striking regularity up to at least the 90th passage, which is the point we have reached at present, and there is barely as yet a slight tendency towards a shorter period of incubation than seven days.

The series was begun in November 1882, and has now lasted three years already. It has never once been interrupted, and never has it been necessary to have recourse to any other than the virus of rabbits of the same series which had previously died of rabies. Nothing is easier, therefore, than to have constantly at one's disposal, for considerable lengths of time, a virus of perfect purity and always identical with itself or as nearly so as possible. Therein lies practically the whole secret of the method.

The spinal marrows of the rabbits are virulent throughout the whole of their substance, with constancy of the virulence. If from those marrows we take portions a few centimetres long, using all possible precautions to keep them pure, and then suspend them in a dry atmosphere, their virulence diminishes slowly until at last it is all lost. The time that the virulence takes to disappear entirely

varies somewhat with the thickness of the marrows, but most of all with the outside temperature. The lower the temperature, the longer is the virulence preserved. These points constitute the scientific part of the method.[1]

After those preliminary explanations, here is the process for rendering dogs refractory to rabies in a relatively short time.

In a series of flasks, the air inside which is kept dry by dropping pieces of caustic potash into it, suspend every day a portion of fresh spinal marrow taken from a rabbit which has died of rabies of seven days' incubation. Every day also inject under the skin of the dog to be made refractory a full Pravaz hypodermic syringe of sterilised broth in which has previously been triturated a small piece of one of the drying marrows. Begin with a marrow old enough to make sure that it is not at all virulent. Previous experimentation will already have settled that point. On the succeeding days proceed in the same manner with fresher marrows, and use those of every second day, until finally we inoculate a last and very viru-

[1] If the rabid marrow be put whilst still moist in an atmosphere of carbonic acid, its virulence can be preserved intact at least for several months, provided we keep it free from admixture with atmospheric or other germs.

lent one which has been drying only one or two days.

The dog has now become refractory to rabies, and will not take it anyhow inoculated, under the skin or on the surface of the brain.

Making use of this method, I had already rendered fifty dogs of all ages and of all races refractory to rabies, without having met with a single failure when, unawares, on Monday, July 6 last, three persons coming from Alsace presented themselves at my laboratory; they were—

Theodore Vone, a grocer from Meissengott, near Schelstadt, bitten on the arm on July 4 by his own dog, which had become mad.

Joseph Meister, nine years old, bitten also on July 4 at eight o'clock in the morning, and by the same dog. This child had been thrown down by the dog and had received numerous bites on the hand, the legs and thighs, some of them so deep that he could scarcely walk. The principal wounds had been cauterised with carbolic acid by Dr. Weber, of Villé, on July 4, at eight o'clock in the evening, twelve hours only after the accident.

The third person was the mother of little Joseph Meister, and had not been bitten.

The dog had been killed by his own master, and on opening his stomach it had been found stuffed with hay, straw, and chips of wood. The animal was certainly mad. Joseph Meister had been rescued from him all covered with saliva and blood. Mr. Vone had been severely contused on the arms, but he assured me that his shirt had not been traversed by the fangs of the dog. I told him there was nothing to fear, and that he could go home that same day, which he did. But I kept with me little Meister and his mother.

The weekly meeting of the Académie des Sciences was held on that same day, July 6. I saw there our colleague Dr. Vulpian, to whom I related what had occurred. Dr. Vulpian, joined by Dr. Grancher, professor at the School of Medicine, kindly consented to come at once and see the state and the number of the wounds of little Joseph Meister. He had been bitten in fourteen different places.

The advice of our learned colleague and of Dr. Grancher was, that owing to the depth and number of his wounds, Joseph Meister was exposed to almost certain death from hydrophobia. I then communicated to Drs. Vulpian and Grancher the

new results I had obtained in my studies of rabies since the time of my lecture in Copenhagen a year before.

The child, being apparently doomed to inevitable death, I resolved, not without feelings of utmost anxiety, as may well be imagined, to apply to him the method of prophylaxis which had never failed me in dogs.

My set of fifty dogs, indeed, had not been bitten before they were made refractory to rabies; but that objection had no share in my preoccupations, for I had already, in the course of other experiments, rendered a large number of dogs refractory after they had been bitten.

I had that same year invited the members of the Commission on Rabies to witness that new and important progress.

On July 6, then, at eight o'clock in the evening, sixty hours after the bites of the 4th, and in the presence of Drs. Vulpian and Grancher, we inoculated into the right hypochondrium of little Meister, under a fold made in his skin, the half of a Pravaz hypodermic syringe containing the marrow of a rabbit which had died rabid on June 21 previous. Since that date the marrow had been kept in dry air, suspended in a bottle—fifteen days altogether.

On the following days the inoculations were renewed, always in the hypochondria and in the manner indicated in the following table: —

July 7 at	9 A.M.	Marrow of	June 23	i.e.	14	days old.
7 ,,	6 P.M.	,,	,, 25	,,	12	,,
8 ,,	9 A.M.	,,	,, 27	,,	11	,,
8 ,,	6 P.M.	,,	,, 29	,,	9	,,
9 ,,	11 A.M.	,,	July 1	,,	8	,,
10 ,,	11 ,,	,,	3	,,	7	,,
11 ,,	11 ,,	,,	5	,,	6	,,
12 ,,	11 ,,	,,	7	,,	5	,,
13 ,,	11 ,,	,,	9	,,	4	,,
14 ,,	11 ,,	,,	11	,,	3	,,
15 ,,	11 ,,	,,	13	,,	2	,,
16 ,,	11 ,,	,,	15	,,	1	,,

The treatment, therefore, lasted ten days, and the total number of the inoculations was thirteen. I shall say later on that a smaller number of inoculations might have sufficed, but in this first case I had necessarily to act with peculiar circumspection.

Two fresh live rabbits were also inoculated on the brain with every one of the marrows used, in order to follow their degrees of virulence.

The observation of those rabbits brought out the following points: the marrows of July 6, 7, 8, 9, 10 were not virulent, for the rabbits inoculated with them did not become mad. The marrows of July 11, 12, 14, 15, 16 were all virulent, in ascending progression. The rabbits inoculated from the marrows of July 15 and 16 took rabies after seven

days' incubation; those inoculated from the marrows of the 12th and 14th after eight days; those from July 11 after fifteen days.

I had, therefore, in the last days of the treatment, inoculated Joseph Meister with the most powerful rabies virus—namely, the virus of the ordinary mad dog, strengthened by a large number of passages through rabbits, a virus giving rabies to rabbits after seven days' incubation, to dogs after eight or ten days only. My action was justified by what I had observed in the fifty dogs of which I have spoken before.

When once the state of immunity has been reached, there is no danger attaching to the inoculation in any quantities of the most powerful virus. It has always appeared to me that the only consequence of such inoculations was to consolidate the refractory state.

Joseph Meister has, therefore, escaped from the hydrophobia which he might have developed in consequence of the bites he had received, and also from the hydrophobia, more powerful than the one resulting from ordinary canine madness, which I inoculated into him to test the immunity imparted by the treatment.

This last highly virulent inoculation has one more advantage: it limits the period of time during

which fears may be entertained as to the results of the bites. If rabies could come on at all it would undoubtedly do so quicker after this most virulent inoculation than after the bites. As early as the middle of the month of August I looked forward with confidence to the future health of Joseph Meister. To-day, three months and three weeks after the accident, his health is still perfect.

What is the mode of action of the new method, just given, of the prophylaxis of rabies after bites? I do not purpose to deal fully with the question to-day, but shall content myself with a few preliminary remarks, which will help to explain the meaning of the experiments which I am still carrying on for the purpose of giving us a clear idea as to the best possible interpretation.

If we consider, on the one hand, the methods of progressive attenuation of mortal viruses and the prophylaxis which can be derived from them, and, on the other hand, the influence of atmospheric air on that attenuation, the first explanation which offers itself to the mind is that the continuous contact of the rabid marrows with dry air progressively diminishes their virulence until it is finally all lost.

It would hence appear that our prophylactic

method rested on the use, first of all, of a virus without any appreciable degree of virulence, and then of viruses progressively virulent, from the lowest up to the highest.

I shall show later on that the facts do not agree with that hypothesis. I shall also give proof that the delays in the incubative periods of the rabies inoculated from day to day into fresh live rabbits, as just indicated, and for the purpose of testing the state of the virulence of our desiccated marrows, are due not to a diminution in the degree of virulence of those marrows, but to a diminution in the quantity of rabies virus contained in them.

Might it be, then, that the inoculation of a virus, the virulence of which should always remain identically the same, could bring on a state of refractoriness to rabies on condition that we proceeded in the use of it by very small but daily increasing quantities? That would be one way of interpreting the facts of the new method, and a way which I am occupied in verifying experimentally.

Yet one hypothesis suggests itself in explanation of the new method: a hypothesis which at first sight seems very strange, assuredly, but one nevertheless worthy of all consideration, for it is in keeping with certain known facts of the vital pheno-

mena observed in several of the lower beings, and, in particular, in certain pathogenic micro-organisms.

A large number of micro-organisms apparently give rise, in the media where they grow, to substances which have the property of opposing their own growth.

As early as the year 1880 I had initiated some researches having for their object to detect some such poison produced by the fowl-cholera micro-organism and toxic to that same micro-organism.[1] I have not been able, as yet, to demonstrate the presence of such a substance; but I am of opinion to-day that those studies ought to be taken up anew, and I shall not fail to do so myself, taking care to cultivate the micro-organism in an atmosphere of pure carbonic acid gas.

The microbe of swine-plague thrives in broths of very varying composition, but it is so rapidly stopped in its development, and the weight of it formed is so small, that it is occasionally barely possible to tell the presence of a crop of it by noticing the slender silky bands undulating in the nutrient medium. It looks as if at once had been produced a substance which had stopped the growth of the little being, whether sown in presence of air or *in vacuo*.

[1] See *Comptes Rendus*, t. xc. 1880.

M. Raulin, once my assistant, and now a professor in the Faculty of Lyons, showed, in the very remarkable thesis which he presented in Paris on March 22, 1870, that the *Aspergillus niger* develops during growth a substance which stops, to some extent, the further production of that mould whenever the nutrient medium does not contain iron salts.

Might it be, then, that rabies virus was made up of two distinct substances, the one living and capable of multiplying in the nervous system, the other not living, but capable still, when in suitable proportions, of arresting the development of the first?

In an early communication I shall give the experimental and critical results arrived at with regard to this third hypothesis concerning the mode of action of the prophylactic method.

It is scarcely necessary in closing to remark that probably the most anxious question for the present is that of the time which may be allowed to elapse between the bite and the application of the treatment. That interval was, in the case of Joseph Meister, two days and a half, but it will certainly be considerably longer in a large number of cases.

On Tuesday last, October 20, obligingly assisted by MM. Vulpian and Grancher, I had to begin the treatment of a young man of fifteen who had been bitten six full days previously on both hands and in circumstances of peculiar gravity.

The Academy will not listen without some emotion to the story of the deed of bravery and of cool-mindedness done by the boy whose treatment I took in hand last Tuesday. Jean-Baptiste Jupille is a shepherd boy belonging to Villers-Farlay, in the department of Jura. Seeing a powerful dog with suspicious gait throwing himself upon a group of six of his comrades, all younger than himself, he seized his whip and rushed forward to meet the animal. The dog at once caught hold of Jupille by the left hand. Then followed a hand-to-hand fight, so to speak, the boy finally throwing down the animal and pinning him to the ground under his knee. Next, with his right hand he forced open the jaws of the beast, disengaged his left hand —all the while receiving new bites—and taking the thong of his whip he tied the muzzle of his enemy and with one of his wooden-shoes beat him dead.

I shall make it a point to acquaint the Academy with the results of this new trial.

VII. *March* 1, 1886.—*Results of the Application of the Method of Prophylaxis of Rabies after Bites.*

On October 26 last I acquainted the Academy of Sciences with a new method for the prevention of rabies after bites, and also with the details of its application to a young Alsatian boy, Joseph Meister, who had been severely bitten on July 4 preceding. The dog was manifestly rabid, and a recent inquiry conducted by the German authorities has again shown that the animal was in a full fit of madness when he bit Meister. The boy is still in perfect health at the present time; his bites date from nearly eight months ago.

At the very time I was reading the note just referred to, I had under treatment the young shepherd boy Jupille, who had been bitten, more severely perhaps than Meister, on October 14. The health of this boy also remains to-day as good as can be desired. He was bitten four months and a half ago.

Soon those two first and successful attempts were bruited about, and a large number of persons who had been bitten by mad dogs repaired to my laboratory asking to be treated like Meister and

Jupille. This very morning—I am writing on Thursday, February 25—assisted by Dr. Grancher, whose devotion and zeal are above all praise, we began the preventive inoculations in the three hundred and fiftieth patient.

Although my laboratory, which has been given up altogether to the study of rabies for the last five years, has been a centre of information for everything appertaining to rabies, I confess that I shared in the general feeling of surprise at seeing such a large number of people who had been bitten by mad dogs. Our ignorance in that respect was due to more causes than one.

As long as rabies had been considered an incurable affection, people tried to keep away from the minds of those who had been bitten the very name of the malady. When a person had been bitten, all at once unanimously declared that the dog was not mad, although the report of the veterinary surgeon or of the medical man should certify to the contrary, and the greatest silence was observed concerning the accident. Coupled with the desire of keeping the mind of the victim quiet there was added, amongst his relatives, the fear of doing him an injury. For people have occasionally gone so far as to refuse to employ workmen who

were known to have been bitten by mad dogs, believing that such persons could, all of a sudden, become dangerous; a groundless fear, fortunately. A man affected with rabies is only to be feared in the last paroxysms of the disease.

In order to carry conviction into the minds of persons who might be prejudiced against the method, or even hostile to it, I have been careful to draw up very rigid statistics, always insisting on the patients bringing with them certificates as to the rabid state of the dog, and delivered by registered veterinary surgeons or by medical men. And yet, all the same, I could not do otherwise, in a few very rare cases, but treat persons who had been bitten by dogs simply suspected of being mad, and which had afterwards disappeared and had never been heard of again. Such persons, in addition to the real danger threatening from the bites received, would have gone on living in a state of perpetual anxiety capable in itself of impairing their health had we refused to intervene.

I did not, however, treat any persons whose garments had not been visibly traversed or torn by the teeth of the animal. It is very evident that in such cases there is nothing to fear, for the virus cannot possibly have got into the system even

though there should be a deep and even a bleeding contused wound. In a certain number of doubtful cases the rabid state of the dog was demonstrated in my own laboratory by inoculations into rabbits and guinea-pigs of the nervous matter taken from the dead animal.

I should like now to give a sufficiently exact idea of the physiognomy of the treatment and also of the nature of the bites by quoting in chronological order one of the series of persons undergoing treatment. It would be fastidious to give details concerning three hundred and fifty cases. I shall therefore make my choice more specially out of the first hundred persons bitten and treated. They comprise the period between November 1 and December 15.

They are particularly interesting, for they have all at the present time got beyond the really dangerous period.

I open my register at the chapter concerning that first hundred, and find in the space of ten days the following variety of cases :—

Etienne Roumier, forty-eight years old, belonging to the parish of Ourouère, department of Nièvre, bitten on both hands on November 4, 1885, by a dog certified to be mad by M. Moreau, V.S. No

cauterisation or dressing of any kind for twenty-four hours.

'*Chapot*, forty-three years old, and his daughter, fourteen years, from Lyons, both bitten on the left hand on November 6, 1885, the girl much more severely than her father. The wounds had been washed with ammonia by a chemist. Dog certified mad by the Veterinary School of Lyons.

'*François Saint-Martin*, from Tarbes, ten years old, bitten on the thumb of the right hand on Friday, November 7, 1885. Wound bathed with ammonia by a chemist. Dog certified rabid by M. Dupont, chief of the sanitary service for animal plagues.

'*Marguerite Luzier*, from Fongrave (Haute-Garonne), thirteen years old, bitten on the leg by a mad cat on November 11, 1885; cauterised with carbolic acid. The gravity of the bites calling for special surgical treatment, the child had to be sent to the Enfants-Malades (Sick Children's) Hospital.

'*Corbillon*, twenty-seven years old, from Neuville, near Clermont (Oise), bitten on November 12, 1885. Dog certified mad by M. Chantareau, V.S. in Clermont. Cauterised with the red-hot iron eight hours after the accident.

'*Bouchet*, five and a half years, living near the

7th sluice of the Saint-Denis Canal, bitten on November 12, 1885, on the left hand and thigh. Trousers torn. Dog certified mad by M. Coret, V.S. in Aubervilliers. Cauterised with the red-hot iron three quarters of an hour after the accident, by Dr. Dumontel.

'*Madame Delacroix*, from Lille (Nord), bitten on November 6, 1885, on the right foot. Cauterised with the red-hot iron nine hours afterwards. Dog certified mad by M. Fréler, V.S. in Lille.

'*Plantin*, from Etrung (Nord), bitten on the right hand in the beginning of November 1885. Cauterised forty-eight hours after the accident. Dog certified mad by M. Eloire, V.S. in Capelle (Aisne).

'*Jeanne Pazat*, seven years, from Mereuil (Dordogne), bitten on November 12, 1885, on the right hand, by a dog certified mad by Dr. de Pindray. The doctor saw her forty-eight hours only after the accident, and rightly judged that it was too late to cauterise.

'*Madame Achard*, from Saint-Etienne, bitten on November 9, 1885, on the right foot, and again on November 12 on the right hand, by the same dog. Dog certified mad by M. Charloy, V.S. in Saint-Etienne. Not cauterised.

'*Madame Alphonsine Legrand*, parish of Baune, in the department of Aisne. Bitten on the chin on November 6, 1885. Dog certified mad by M. Decarme, V.S. in Château-Thierry. Not cauterised.

'*Antoine Cattier*, forty-three years old, living at No. 12 rue des Hospitalières Saint-Gervais, Paris, bitten on the hand on November 10, 1885. Cauterised with the red-hot iron twenty hours only after the accident. Dog recognised to be mad by his own master: rabid voice, refused to take any food, all the while tearing and swallowing chips of wood and other objects.

'*Ternat, his wife, Madame Delzors, Madame Dalibard*, all four bitten on November 15, 1885, by the same dog, recognised to be mad while still alive, and then certified so after death by the well-known Saint-Ouen V.S. Sanfourche. Cauterisations insignificant and tardy.

'*Doctor John Hughes*, from Oswestry (England), bitten on November 13, 1885. Two deep wounds in the lower lip. Not cauterised. Dog certified mad by the doctor himself.

'*Widow Faure*, from the village of Alma, Algeria, bitten on the leg on November 1, 1885; garments torn by the same dog, which bit the four children known as 'of Algeria,' of whom one died in

the Mustapha Hospital in Algiers two months after the accident. The rabid symptoms presented by this child were very carefully described by Dr. Moreau, of Algiers. The prophylactic treatment was applied to the three other children in the middle of November.

Madame Gréteau, from Bordeaux, bitten on November 14, 1885. Two bites on the ring finger of the right hand, one in the fleshy part of the last phalanx, the other on the nail, which was cut in two about its middle. Dog certified mad by Dr. Douaud. Wounds bathed with ammonia and slightly cauterised.

'*Voisenet* (*Noël*), from Semur (Côte-d'Or), fifty years; bitten on November 6, 1885, on both legs by a bitch certified mad by M. Colas, V.S. Cauterised with the hot iron four hours only after the bites.

'*Guichon*, from Bordeaux, sixty-seven years, bitten on November 15, 1885, on the left hand, by the same dog which bit Madame Gréteau, above mentioned.

'*Halfacre* (*Walter*), from London, twenty-eight years, bitten on the hand on November 15, 1885, and sent to us by Dr. James Paget. Not seriously cauterised. The brother of Halfacre died of hydro-

phobia five years ago in consequence of a bite which appeared so insignificant that it was left unnoticed.

'*Calmeau*, from Vassy-lez-Avallon, bitten on the night of November 15–16, 1885, on the abdomen, on the thigh, on the knee; dress and shirt in shreds. Not cauterised at all. Bitch certified mad by M. Colas, V.S. in Semur. This is the same bitch which had bit Voisenet (Noël) above mentioned.

'*Lorda* (*Jean*), thirty-six years, from Lasse (Basses-Pyrénées). This case is most interesting. Lorda was bitten on October 25, 1885, but only came to my laboratory on November 21, the twenty-fifth day after the accident. On the same day as himself, and by the same dog, seven pigs and two cows were also bitten. The nine animals have died of rabies, the pigs after a short incubation of from fifteen to twenty-one days. It was only after the death from rabies of the pigs that Lorda took fright and left for Paris.

'The first cow died thirty-four days after she had been bitten, the second one fifty-two days after. I am indebted for the details of these curious facts to M. Inda, the able V.S. of Saint-Palais. One observation of his report is specially worth noting: the two cows had been thoroughly cauterised with the red-hot iron immediately after the accident; he

underlines that particular point. I have had sufficiently numerous proofs of the inefficiency of cauterisation in certain cases, even though made with the hot iron and immediately after the bite. The health of Lorda is still keeping excellent. His treatment was finished on November 28 last.'

Such is the enumeration, in the chronological order of their arrival at my laboratory, of twenty-five bitten persons comprised in a period of ten days. All other periods of ten days would offer sets of cases the enumeration of which would not teach us more than the last one, although in each one we might meet with one or more cases of bites no less interesting than that of Lorda.

But I shall make short, and cite just one more of those cases because it was the cause of great anxiety to me. It is that of a young boy called Jullion, living at Charonne, rue des Vignolles, No. 6, and bitten on November 30. This child, seeing the dog come up to him, began to cry. At this very moment the dog thrust his lower jaw into the open mouth of the child. One of the fangs, cutting the upper lip, penetrated deeply into the hard palate, meanwhile one of the teeth of the upper jaw which had remained outside the child's mouth tearing in between the right eye and the nose. It was here

impossible to cauterise. This dog was certified mad by M. Guillemard, V.S., rue de Citeaux, Paris.

In one case alone has the treatment failed: that of the young girl Louise Pelletier, who died of rabies after she had been treated. This child, ten years old, had been bitten on October 3, 1885, at la Varenne-Saint-Hilaire by a large mountain dog, and brought to me on November 9 following, thirty-seven days only after the accident, the bites being deep and situated in the pit of the axilla and on the head. The bite on the head was so serious and so extensive that on November 9 it was still discharging pus and blood, although the child had all the time been under medical care. It measured 12 centimetres by 15 (a centimetre is 0·39370 of an English inch) and at one place the skin was still hanging loose. This wound made me feel very anxious, and I asked Dr. Vulpian to come and examine it. In the scientific interest of the method I ought to have refused to treat that child who had come so late and in circumstances of such exceptional gravity; but I should not have forgiven myself had I not tried everything, and I yielded to a feeling of humanity, moved also by the anguish and entreaties of the parents.

Premonitory symptoms of hydrophobia showed

themselves on November 27, eleven days only after the end of the treatment; they became more marked on the morning of December 1, and death, accompanied by the most marked symptoms of rabies, closed the scene on December 3 in the evening.

Now arose an all-important question: which of the two rabies viruses had brought on death, that of the dog-bite or that of the prophylactic inoculations? It was easy to know. Twenty-four hours after the death of Louise Pelletier, with the authorisation of the parents and of the Préfet de Police, the skull was trephined in the region of the wound, and a small quantity of cerebral or brain matter was taken out and inoculated intra-cranially into two rabbits. The two rabbits were seized with paralytic rabies eighteen days afterwards, and both in the same hour. After their death their medulla oblongata was inoculated into fresh rabbits, and these took rabies after an incubation of fifteen days. These experimental results suffice to demonstrate that the virus which proved fatal to the girl Pelletier was the virus of the dog that had bitten her.

Had death been the result of the preventive inoculations, the incubation after this second inoculation into rabbits would have been seven days at

most. This is established by the explanations given in my last note to the Academy.

But although the preventive treatment in 350 cases has never once given rise to untoward results, not a single inflammatory swelling, not a single abscess, barely a little œdematous redness after the last inoculations, are we yet authorised in saying that it has shown itself actually efficacious in preventing the development of rabies after bites? Considering the large number of persons treated, one eight months ago (Joseph Meister), another more than four months since, and for the majority of the 350 others we are authorised in saying 'Yes, the method has given proof of its efficacy.'

This assertion is best justified by a comparison with the average number of cases of rabies developed after rabid bites. Works on human and on veterinary medicine do not agree very well on that point. The discrepancy is easily understood if we consider what I said a few moments ago with reference to the silence so often kept by families and by medical men as to the existence of bites by rabid animals and even as to the nature of the cause of death, designated, wittingly at times, under the name of *meningitis*, when it is well known to have been due to rabies.

The difficulty of getting up trustworthy statistics is well exemplified by the following case: On July 14, 1885, five persons were bitten by the same mad dog on the road to Pantin. The five persons took rabies and died. Dr. Dujardin-Beaumetz was thereupon appointed by the Prefect of Police to investigate the case and report to the Conseil de Salubrite de la Seine (Board of Health of the Seine department) the names and all the circumstances concerning the bites and the death of those five persons. Let such a series enter into the constitution of statistics, and at once the proportion of deaths to bites will rise. On the contrary, let such a series, where out of five persons bitten not one had died, be included in it, and the proportion will be lowered. I would place greater confidence in the following statistics, drawn up by M. Leblanc, the learned V.S., member of the Academy of Medicine, and for a long time chief of the sanitary department at the 'Préfecture' of Police. He was good enough to let me have a copy of a valuable document on the subject of which we are speaking. It is an official abstract made by himself, and based on the reports of the commissaries of police and on information supplied by veterinary surgeons managing hospitals for dogs. It covers a space of

six years, and shows that for the department of the Seine there were—

Year	Persons Bitten	Deaths by Rabies
1878	103	24
1879	76	12
1880	68	5
1881	156	23
1882	67	11
1883	45	6

Those numbers give on the average one death by rabies for six persons bitten—one in six.

But one more question, no less capital than that of the average number of deaths after rabid bites, remains to be solved yet before we can rightly estimate the efficacy or otherwise of the method of prophylaxis. It is necessary, namely, to know whether the time elapsed since the occurrence of the accident is long enough to justify us in considering the persons treated as having got beyond the period when rabies may yet break out. In other words, how long after a rabid bite does hydrophobia manifest itself?

Statistics show that rabies breaks out oftenest within the first two months—that is to say, between the fortieth and sixtieth days after the bites. Now, of those persons, of all ages and of either sex, already treated by the new method, 100 had been

bitten before December 15, more than two months and a half since. The bites of the second hundred date farther back already than six weeks and two months. For the remaining 150 persons treated or still under treatment all is going on, so far, as well as for the 200 first ones.

It is evident, therefore, by comparison with the most searching statistics, that a considerable number of persons have already been snatched from death.

The prophylactic treatment of rabies after bites is henceforth an established fact.

There is cause enough to found a special establishment for vaccination against rabies.

VIII. *April* 12, 1885.—*Further Results of the Method of Prophylaxis of Rabies after Bites.* On March 1 last, I acquainted the Academy with the results arrived at by the method of prophylaxis of rabies after bites of rabid animals; it had at that date been applied to 350 persons of all ages. To-day, April 12, the total number of such persons who have been treated or are still under treatment amounts to 726, and can be grouped according to nationality as follows:—

France	505
Algeria	40
Russia	75
England	25

Italy	24
Austria-Hungary	13
Belgium	10
America (North)	9
Finland	6
Germany	5
Portugal	5
Spain	4
Greece	3
Brazil	1
Switzerland	1
Total	726

That list is made up itself of two others which it is essential should be considered separately.

The first one comprises the persons bitten by mad dogs; the second one, those bitten by mad wolves.

The number of persons treated after bites of mad dogs comes up to 688.

The number of persons treated after bites of mad wolves comes up to 38.

If this distinction were left out of sight, we should run the risk of passing erroneous judgment on the method of prophylaxis of rabies.

The 688 persons treated who have been bitten by mad dogs are all alive and well to-day (if we still except the case of the girl Pelletier). And yet more than one-half of them have now got beyond the dangerous stage.

Of the 38 Russians who have been treated or who are still undergoing treatment and who had been bitten by mad wolves, three have died of rabies; the others are well, so far, but it is impossible to foresee how they may fare ultimately, for, as a matter of fact, there are great differences as to their consequences, between the bites of dogs and the bites of wolves.

Several persons have had the kindness to communicate to me the very authentic records of cases of bites by mad wolves, and I think it may be useful to give here the conclusions of their reports.

First Document.—On February 27, 1706, eight persons belonging to the parish of Saint-Julien-de-Civry, in Burgundy, were bitten by a mad wolf.

One of them died the same day in consequence of the intrinsic gravity of the wounds he had received; the remaining seven all died of rabies after incubative periods which ranged from seventeen to sixty-eight days (17, 26, 28, 42, 44, 60, 68 days). (Borrowed from the death-register of the parish by M. Sandre, schoolmaster, the copy certified true by the mayor of the parish).

Second Document.—On December 26, 1806, in the neighbourhood of the town of Bourg, nine persons were bitten by a mad wolf; eight of them

died of rabies. This case is reported by Dr. Lutil-Thimécour, of Lyons, who mentions the duration of incubation for one of the victims, an old woman of sixty, Claudine Tabouet, as having been twenty-four days. He adds that the others died soon after, and at short intervals.[1]

Third Document.—On October 16, 1812, nineteen persons were bitten by a mad wolf in the town of Bar-sur-Ornain. They were all treated by Doctors Champion and Moreau, who washed their wounds and cauterised them with liquid muriate of antimony.

Eleven of those persons died of rabies after an incubation time which varied from seven, thirteen, and fifteen days, to sixty, sixty-nine, and seventy days. (From a communication made by Dr. Champion to the Institut de France on September 6, 1813.)

Fourth Document.—On February 23, 1840, a shepherd of Darbois, called Dumont, aged sixty-four years, was bitten by a mad wolf. He died of rabies after an incubation of thirty-two days. (Communicated by MM. Caillebet and Mariotti.)

Fifth Document.—On January 7, 1866, three

[1] We have taken the liberty of altering slightly the text by inserting the information contained in the last six lines—which the *Revue Scientifique* published after the date of the present communication.—AUTHOR.

persons belonging to the neighbouring parishes of Nant, Alques, and Saint-Jean-du-Bruel, in the department of Aveyron, were bitten by a mad she-wolf. They all three took rabies and died after incubations of twenty-two, twenty-three, and thirty-eight days respectively. (Communicated by Dr. Bompaire, of Millau, Aveyron.)

Sixth Document.—On October 5, 1874, in the parish of Rochette, canton of La Rochefoucauld (Charente), two men were bitten by a mad wolf which had just previously thrown down and torn up a little girl.

Both men took rabies and died, after incubative periods respectively of twenty-five and thirty days. The little girl died of her wounds on the day she received them. (From the newspaper *Le Charentais*, October and November, 1874.)

Seventh Document.—In a letter written on March 26 last, Dr. Niepce, medical officer to the mineral-water station of Allevard, gave to Dr. Vulpian an account of four cases of bites by a mad wolf, in 1822. All four persons died of rabies after incubations of nine, thirteen, fifteen, and nineteen days.

Eighth Document.—On May 11 and 12, 1811, in the neighbourhood of Avallon, a mad wolf bit several persons and a large number of cattle.

All the persons bitten took rabies, and died on the following dates, as seen in the death-register of the hospital :—

In May 1811, on the 24th, 27th, 28th, 30th (two deaths), 31st ; and therefore thirteen, sixteen, seventeen, nineteen, and twenty days after the bites. (Copied from the registers of the hospital of the town of Avallon, department of Yonne.)

By adding together those eight documents we get a percentage of deaths after the bites of mad wolves of eighty-two per cent. ; and, in six cases out of the total of eight, there were as many deaths as there were persons bitten. Were we to apply the same percentage of deaths to the nineteen Russians from Smolensk whose treatment is now ended, and of whom sixteen are leaving to-day for Russia, it is not three deaths from rabies that we should have had to deplore, but fifteen or sixteen. It is beyond doubt that the treatment must have shown itself efficacious for the majority of them.

Yet more : the consensus of opinion in Russia is that every person bitten by a mad wolf is inevitably doomed to death by rabies.

The facts just recorded show :

1. That the incubation of rabies in man, following upon bites of mad wolves, is often very

short, considerably shorter than the incubation after bites of mad dogs.

2. That the death-rate after bites of mad wolves is considerable when compared with the death-rate after bites of mad dogs.

Those two propositions find sufficient explanation in the great number, the depth and the seat of the wounds made by the wolf, which fastens itself to its victim, often attacking him on the head and face. The necropsy of the three Russians who succumbed at the Hôtel-Dieu and the inoculation into dogs, rabbits, and guinea-pigs of the medulla oblongata of the first one of them who died, show that wolf-virus and dog-virus are sensibly of the same strength, and that the difference between wolf-rabies and dog-rabies is owing in the main to the number and nature of the bites.

Those facts have induced me to investigate whether the method might not be usefully modified, after wolf-bites, by inoculating larger quantities of the vaccinating virus and at shorter intervals of time. I shall later on acquaint the Academy with results.

In any case, and after wolf-bites in particular, it is well to come for prophylactic treatment as early as possible. The Smolensk Russians were six

days on the way, and only arrived at the laboratory fourteen and fifteen days after they had been bitten. It would therefore have been possible, at a stretch, to commence their treatment eight days earlier, and it is now impossible to say what difference that might have wrought for the three who have succumbed.

IX. *November* 1, 1886.—*New Communication on Rabies.*—On October 26, 1885, I acquainted the Academy with a method of prophylaxis of rabies after bites. Numerous applications on dogs had justified me in trying it on man. As early as March 1, 350 persons bitten by dogs undoubtedly mad, and several more by dogs simply suspected of rabies, had already been treated at my laboratory by Dr. Grancher. And in consideration of the happy results obtained it appeared to me that it had become necessary to found an establishment for anti-rabic vaccinations.

To-day, October 31, 1886, 2,490 persons have received the preventive inoculations in Paris alone. The treatment was in the first instance uniform for the great majority of the patients, notwithstanding the different conditions presented by them as to age, sex, the number of bites received, their seat, their depth, and the time which had elapsed

since the occurrence of the accident. It lasted ten days, the patient receiving every day an injection prepared from the spinal marrow of a rabbit, beginning with that of fourteen days' and ending with that of five days' desiccation.

Those 2,490 cases are subdivided according to nationality in the following manner :—

Russia	191
Italy	165
Spain	107
England	80
Belgium	57
Austria	52
Portugal	25
Roumania	22
United States	18
Holland	14
Greece	10
Germany	9
Turkey	7
Brazil	3
India	2
Switzerland	2
France and Algeria	1,726

The number of French persons has been considerable, amounting to 1,726, and it will be enough to confine ourselves to the category formed by them as a basis for discussing the degree of efficacy of the method.

Out of the total 1,726 cases treated, the treat-

ment has failed ten times—namely, in the following cases:—

The children: Lagut, Peytel, Clédière, Moulis, Astier, Videau.

The woman: Leduc, seventy years old.

The men: Marius Bouvier (thirty years), Clergot (thirty), and Norbert Magnevon (eighteen).

I leave out of count two other persons, Louise Pelletier and Moermann, whose deaths must be attributed to their tardy arrival at the laboratory, Louise Pelletier thirty-six days, and Moermann forty-three days after they had been bitten.

We have therefore ten deaths for 1,726 cases, or 1 in 170; such are, for France and Algeria, the results of the first year's application of the method.

Those statistics, taken as a whole, demonstrate the efficacy of the treatment, as proved further by the relatively large number of deaths which occurred amongst bitten persons who had not been vaccinated. We may state as a fact that of all French people bitten by mad animals in this year 1885–1886, very few were those who did not come for treatment to the laboratory of the Normal School. And yet, out of that small minority, there have been, to my own knowledge, no less than

seventeen deaths by rabies. I give them in a footnote.[1]

[1] 1. The mayor of Tourcoing acquaints me with the death from rabies on December 12, 1885, of a child called Saumyn (François). He was bitten on the same day and by the same dog as Mésiaux (Jacques-Louis) in November 1885. Mésiaux was treated at my laboratory and is still in good health, but they had neglected to send on Saumyn.

2. Four children belonging to the convent of Alma, near Algiers, were bitten on August 31, 1885. One of them, not treated by the inoculations, died of rabies in the civil hospital of Algiers. The remaining three were vaccinated in November 1885, and are still well.

3 & 4. The husband and father-in-law of Céline Lagaz, of the parish of Vooray (Haute Savoie), not vaccinated, died of rabies within the same week. Céline Lagaz was vaccinated in November 1885, and is still well.

5. Harembure, surnamed Larralde, not vaccinated, died of rabies on January 21, 1886, at Amoratz-Laccos, in the Basses-Pyrénées.

6. Malandain (Ernest), from Daubeuf-Serville (Seine-Inférieure), came for treatment in August 1886, after he had seen a woman belonging to the same parish, and who had been bitten by the same dog and on the same date as himself, die of rabies. The woman had not been inoculated; he is still alive and well.

7. Henri Riffiondi, an Italian, died of rabies last April, in the Beaujon Hospital. In the month of February preceding he had received a slight wound from a mad dog, and, imprudently judging that he was in no danger, did not come for treatment.

8. Widow Busson, from Voujancourt (Doubs), and still alive, applied for treatment after she had on June 17 seen one of her neighbours die of rabies.

9. M. Jamin, the father, belonging to the department of La Sarthe, was bitten on June 25; he was not inoculated, and showed the first symptoms of rabies on August 7 following. Whereupon his son Henri Jamin, Alfred Moermann, and Marie Touchard, who had all three been bitten on the same date as Jamin the father,

The following document forms a natural appendix to our statistics:

The number of persons who die of rabies in the Paris hospitals is very accurately known, particularly so for the last five years.

By order of the Prefect of Police, every case of rabies presenting itself in any one of the Paris hospitals is at once reported by the hospital manager to Dr. Dujardin-Baumetz, member of the Board of Hygiene and of Salubrity of the Seine, who has charge to investigate and send in a report to the Board. It is thus accurately known that in the last five years sixty persons have died of rabies in the Paris hospitals; on an average twelve yearly. No one year has been exempt from such deaths, more or less numerous. Last year they amounted to twenty-one. Now, since November 1,

left for Paris, where their treatment was begun on the forty-third day after the accident. After this tardy arrival, and in spite of the treatment, Moermann took rabies and died.

In addition to those nine persons, there have also died of rabies in Marseilles, the young girl Masson; in Paris, at the Hôtel-Dieu, the man Raffin; the policeman Carpier; Jules L'Hote; a child from Vervins; Mlle. Ganet, who died in the train, tardily coming up to the laboratory for treatment.

Drs. Tueffard and Beucher have, in addition, informed me of the death from rabies of two persons who had not undergone the preventive treatment.

Total: 17 persons, not inoculated, who have died of rabies.

1885, when the preventive treatment began to be applied at my laboratory, only three persons have died of rabies in the Paris hospitals, of whom two had not been inoculated,[1] and the third who had been treated had yet not received the intensive and repeated treatments of which I shall speak in a few moments.[2]

On studying the preceding facts we find that the larger number of those who succumbed, notwithstanding that they had been treated, were young children and had been bitten on the face. They had only received the simple treatment. I have now become convinced that this treatment may occasionally prove insufficient, for such severe bites especially. Unfortunately, such a conclusion could only be come to gradually and after a long time, protracted delays being necessary before concluding, owing to the exceptionally long incubation of rabies in certain cases.

The case of the Smolensk Russians gave us a first indication.

Dr. Grancher and myself were very much distressed on seeing three of the nineteen Russians who had been bitten by a mad wolf die of rabies

[1] Raffin (Hôtel-Dieu); Riffiondi (Beaujon Hospital).
[2] Clerjot (Tenon Hospital).

in the Hôtel-Dieu, the first one while still under treatment, the two others a few days after their treatment was ended. Were, then, the remaining sixteen going to die also? Was the method thus proving powerless against wolf-rabies? Remembering, then, that all the dogs that I had successfully vaccinated had received, as a last preserving inoculation, the virulent marrow taken out of the rabbit on the same day, and also that the first person vaccinated, J. Meister, had completed his treatment with a marrow dating from the previous day only, we submitted the sixteen Russians to a second and then to a third course of treatment, including each time the freshest marrows, those of four, three, and two days.

It is very likely to those repetitions of the treatment that we must attribute the cure of those sixteen Russians. This morning again I have received a telegram saying they are still in excellent health.

Encouraged by those results, and also by certain new experiments of which I shall give the details further on, I have modified the treatment and made it more rapid and more active for all cases, and more rapid and energetic still for bites on the face, and for deep and multiple bites on exposed surfaces.

And actually, for bites on the face or head, and deep bites on the limbs, we precipitate the inoculations and come promptly to the freshest marrows.

Thus, on the first day, inoculate marrows of twelve, ten, and eight days at 11, 4, and 9 o'clock; on the second day, marrows of six, four, and two days at the same hours; on the third day, the one-day old marrow. Then begin the treatment again on the fourth day with marrows of eight, six, and four days; on the fifth day use the marrows three and two days old; on the sixth day, the one day old marrow again. On the seventh day again the four days old marrow; on the eighth day, the three days old marrow; on the ninth day, the two days old marrow; on the tenth day, the one day old marrow. In that manner give three courses of treatment in ten days, carrying each one of them up to the freshest marrows.

If the bites have not yet healed up, or if the patients have only come up tardily for treatment, we often enough, after allowing them two or more days' rest, begin anew the same courses of treatment until we have reached the fourth or fifth weeks, which are the dangerous period for children bitten on the face.[1]

[1] For cases in which the bites are multiple and very severe,

This new mode of vaccination has been applied for the last two months in all very severe cases, and the results are so far extremely favourable. It will be sufficient, in order to show the correctness of my assertion, to compare on the one hand the circumstances of the bites and inoculative treatment of the six children whom the simple treatment failed to save, and on the other hand those relating to ten children who were bitten quite as severely in the month of August last, and who received the intensive treatment. (See Table A, B.)

The dangerous period rarely lasts beyond the fourth or sixth week for children bitten on the head and face, and I am, therefore, confident that those ten children have already got beyond the reach of the disease.

This new treatment has been naturally followed by an increase of work. Dr. Terrillon, professeur agrégé at the Faculty of Medicine; Dr. Roux, sub-manager of my laboratory; Dr. Chantemesse, hospital-physician, and Dr. Charrin, have all lent Dr. Grancher and myself their most zealous collaboration.

the first treatment might be finished in a single day, and then repeated on the following days. Experiments on dogs would justify such a practice. In Russia such exceptionally severe wounds are frequent enough, inflicted by wolves or even by dogs.

A. List of the Six Children who died, out of the 1,700 French people treated, in the First Year (1885–86).

Names	Age	Bites and their seat	Date of bite	Date of treatment	Inoculations	Date of death	Remarks
Videau . .	3 years	Right wrist, right [illegible]	Feb. 24	Feb. 27 to March 7	Marrow 14 to 6 days old; one a day	Sept. 24, 1886	The treatment was insufficient, and only produced partial vaccination
Lagut . . .	11 years	Lower lip	May 18	May 21 to June 2	Marrow 14 to 5 days old	June 17	Ditto
Clédière . .	21 months	Palmar surface, and 2 fingers of right hand	June 17	June 21 to 30	Marrow 14 to 5 days old	Aug. 17	Ditto
Peytel . .	6 years	Ring and middle fingers of right hand, 2 bites at the angle of the mouth, bites on the lower lip, on lid of left eye, on left cheek	June 28	June 30 to July 9	Marrow of 14 to 5 days, then of 10 to 3 days; one marrow a day	July 17	It would have been necessary to give three courses of treatment, inclusive each time of marrows 2 and 1 day old
Moulis . .	6 years	Three bites on the forearm. Great loss of substance	July 31	Aug. 6 to 12	Marrows of 14 to 4 days old; one a day	Sept. 8	Treatment insufficient
Antier . . .	2 years	Two bites on the cheeks just below the eyes, 6 bites about the lips; scratches on both hands	Aug. 1	Aug. 5 to 21	Marrows of 12 to 5 days, then of 8 to 3 days, then of 3 and of 2 days; [illegible]	Sept. 16	Owing to the gravity and to the number of the bites, the first treatment ought to have been completed in one or two days, and to have then been followed by repeated intensive treatments

B. List of Ten Children, bitten on the Face and Head, who were submitted to the Repeated and Intensive Treatment.

Name	Age	Bites and their seat	Date of bites	Date of treatment	Inoculations	Remarks
Degoul	2½ years	Deep bites on head and thighs; 24 bites and scratches altogether	Aug. 29	Aug. 30 to Oct. 2	Marrows 10 to 2 days old inoculated in 3 days Marrow of 8 to 2 days „ 8 „ 1 „ „ 6 „ 1 „	On November 1 it is 63 days since the bites were inflicted
Baillet (Elise) .	3½ years	Several bites below the left eye	Aug. 20	Aug. 22 to Oct. 4	Marrows 14 to 2 days old, given in 3 days; then marrows of 8 to 1 day; then marrows of 6 to 1 day old	Ditto 72 days
Cuningham . .	7 years	Bites on left arm and on left ear	Aug. 23	Aug. 26 to Sept. 23	Marrows 14 to 2 days old; then marrows 8 to 2 days old; then marrows 8 to 1 day old	Ditto 69 days
Tatterall . . .	10 years	Deep bite on left cheek just below the eye	Aug. 7	Aug. 12 to Sept. 13	Marrows 14 to 3 days old „ 8 „ 2 „ „ 8 „ 2 „ „ 8 „ 2 „	Ditto 85 days
Sykes	11 years	Large wound on left cheek	Aug. 22	Aug. 30 to Oct. 2	Marrows 14 to 2 days old, given in 3 days; then marrows of 8 to 2 days; then marrows of 8 to 1 day; then marrows of 6 to 1 day	Ditto 70 days

B. List of Ten Children, bitten on the Face and Head, who were submitted to the Repeated and Intensive Treatment—*continued.*

Name	Age	Bites and their seat	Date of bite	Date of treatment	Inoculations	Remarks
Champion . . .	2½ years	Bites just below left eye, and also on upper lip	Aug. 30	Sept. 1 to Oct. 2	Marrows 12 to 2 days old, given in 3 days Marrows of 8 to 1 day „ 6 „ 1 „	Ditto 62 days
Masson	12 years	Bite on middle part of upper lip	Aug. 26	Sept. 1 to Oct. 3	Marrows 10 to 2 days old, given in 3 days; then Marrows of 8 to 2 days „ 6 „ 1 „ „ 3 „ 1 „	Ditto 66 days
Berthelot . . .	14 years	Bite	Aug. 25	Sept. 2 to Sept. 22	Marrows 12 to 2 days old, given in 3 days; then Marrows of 8 to 2 days „ 5 „ 1 „ „ 4 „ 1 „	Ditto 67 days
Lescure	8 years	Bite at external end of right eyebrow	Aug. 13	Aug. 24 to Sept. 23	Marrows 12 to 2 days old, given in 3 days; then Marrows of 10 to 2 days „ 8 „ 3 „ „ 4 „ 1 „	Ditto 79 days
Dabarry . . .	2½ years	Bite on upper lip, both skin and mucous membrane being implicated	Aug. 20	Aug. 25 to Oct. 1	Marrows 14 to 2 days old, given in 3 days; then Marrows of 8 to 2 days „ 6 „ 1 „ „ 3 „ 1 „	Ditto 72 days

It now remains for me, finally, to give to the Academy the results of certain new experiments on dogs.

Some had objected to our human vaccinations after bites, as usually practised, and based in the main on the vaccination of dogs before bites, that the immunity of animals had not been sufficiently demonstrated after they had previously and with certainty been infected with the virus of rabies. The objection is sufficiently answered if we succeed in producing the refractory state in dogs after trephining and intra-cranial inoculation of the virus of ordinary canine madness, this being the most certain and unfailing mode of infection.

My first experiments on this particular point date from the month of August 1885. Success had at that time been but partial. I resumed the experiments within the last few months, as soon as the organisation of the new treatment gave me the time. They prove successful on the following conditions: the vaccination must begin soon after the infective inoculation, as early as the next day, and must be carried out rapidly, giving the whole series of prophylactic marrows in twenty-four hours or less; then repeat the treatment once or twice, giving one inoculation every two hours.

If Dr. von Frisch (of Vienna) was not successful in this order of experiments, his failures must be attributed to the fact that he used the slow process of vaccination. In order to be successful, it is necessary, I repeat, to act promptly, to vaccinate the animals in a few hours and then to revaccinate them. We might formulate in the following manner the conditions of success or of failure in those experiments: the success of animal vaccination after their intra-cranial infection depends upon the rapidity and intensity of that vaccination.

The immunity conferred under such conditions is the best proof of the excellence of the method.

This is the last of M. Pasteur's communications to the Academy on the subject of rabies. We have, however, one more note from him published in the first number of the monthly 'Annales de l'Institut Pasteur,' addressed to the editor, Prof. Duclaux, and dated from Bordighera, in Italy, December 27, 1886. We shall give here a translation of those portions of the letter which refer to the mode of action of the prophylactic inoculations; the remainder will come more naturally under the heading of statistical results further on:—

What idea can we form as to the cause of the immunity conferred by the method of prophylaxis after bites? On first thought it appears very natural to suppose that the intensity of the virulence of the rabid marrows diminishes progressively, and is at last all lost by their stay in a dry atmosphere at a temperature of 23° C. to 25° C. (about 75° F.). This would then lead to the belief that the method was based on the use at first of a virus without any appreciable degree of virulence, then of one with a feeble degree of virulence, and finally stronger and stronger ones. Notwithstanding the reserves I had made in that connection in my note of October 26, 1885, to the Academy of Sciences, that explanation seems to have very generally prevailed. It has been frequently expressed. All appearances are in favour of it, I must confess, seeing that rabid marrows, dried at 23° C. to 25° C., and then inoculated intra-cranially into rabbits, give rise to rabies in them after periods of incubation the length of which varies directly with the time of exposure in the dry atmosphere. In the practical application of the method it does seem then that the first non-virulent marrows are followed by progressively more virulent ones. But experimentation shows, I believe, that those delays in the time of incubation

are a result of the diminution in quantity of the rabies virus which is dying out rather than a diminution in the degree of its virulence. Suppose, for instance, we take some virus from rabbits with protracted incubation periods—protracted to one month and even more—and inoculate it by trephining into healthy live rabbits, we in all cases at once reproduce our seven days' incubation rabies.[1] The rule is absolute. In practice, then, it does not seem that we have to deal with weaker and then with progressively stronger viruses, but rather with a virus of unvarying intensity, ruled indeed by the law which will have it so, that the duration of incubation varies inversely with the quantity inoculated, the

[1] It might be objected to the hypothesis I am propounding that the splenic fever vaccine fluid resumes all its virulence when, by accident, it causes the death of a sheep or cow. It might also be argued that the heated splenic fever germ, which becomes vaccinal at 55° C., recovers its virulence by one single culture. It will be worth while, nevertheless, to try and see if the refractory state can be produced by inoculations of very small quantities of fully virulent rabies virus, and daily increasing the dose. I may at once say, however, that this process is not vaccinal in the case of splenic fever. The sheep thus treated are not rendered refractory; they are killed, although more slowly than by inoculations of larger quantities.

Let us not lose sight, finally, of the very original and very fruitful theory put forward by Mr. Metschnikoff. Does the vaccinal matter, supposing it to exist, reside in the dead micro-organisms?

virus remaining the same. Thus, the smaller the quantity used the longer the incubation, and *vice versâ*.

The facts agree better with the notion of a vaccinal matter which we may suppose associated with the rabies microbe, the latter preserving its own virulence intact in all the drying marrows. But the process of desiccation destroys the microbe itself progressively and more rapidly than it destroys the vaccinal matter. This opinion is further supported by the following facts:

All methods for the inoculation of rabies, with the sole exception of subdural inoculation after trephining, sometimes, we might almost say often, give rise to a rabies-refractory state without any previous apparent symptoms of an attenuated form of the disease. I could quote numberless instances, but a few will suffice.

1. On February 12, 1885, six healthy dogs receive under the skin of the abdomen a hypodermic syringeful of sterilised broth holding in suspension portions of the triturated medulla oblongata of a dog which had recently died of rabies in the Alfort Veterinary School. On March 6 one of the six dogs takes furious rabies, with well-marked rabid bark.

On March 24 the remaining five dogs are still well and receive intra-cranial inoculations of the virus of ordinary street madness. Three of the five dogs developed rabies on April 4, 5, and 10, whilst the two others remained refractory, a state for which they were owing, evidently, to the subcutaneous inoculations they had received on February 12.

2. On July 23, 1886, seven new dogs are inoculated under the skin of the abdomen, receiving each a syringeful of the sterilised broth holding in suspension part of the medulla of a rabbit belonging to the forty-seventh passage through rabbits. The first rabbit of the series had been infected with the virus of a dog which had died of ordinary canine madness.

On August 5 following, two of the seven dogs show symptoms of dumb-madness, and lie down without attempting to bite and voiceless. On the following day the same symptoms develop themselves in a third dog, in a fourth one next day, in a fifth on August 10, in a sixth one on August 25. The seventh dog does not fall ill either in August or in September. In order to ascertain whether he is now refractory in consequence of the inoculation received on July 23, he is trephined and receives on

the surface of the brain a quantity of the virus of an ordinary mad dog. He does not evince any signs of uneasiness, and remains well all through the succeeding months. He is refractory.

3. On July 31, 1886, seven new dogs receive under the skin of the abdomen the ordinary injection prepared from the medulla of an ordinary mad dog. Five of those dogs took rabies; the first one on August 17, biting madness, with paralysis of the hind quarters, the second one on August 19, the third, fourth, and fifth on August 28 and September 3, all four taking dumb-madness. The remaining two are still well at the end of September, at which date they both receive intra-cranial inoculations with the virus of ordinary street-dog rabies. Several months later they are still keeping perfectly well. They had, therefore, been rendered refractory by the inoculations made on July 31.

4. On January 23, 1885, six new dogs receive under the skin of the abdomen the half of a hypodermic syringeful of the broth holding in suspension the triturated medulla of a rabbit belonging to the sixty-sixth passage of the rabbit series. Five of those dogs took dumb-madness on the eleventh, twelfth, and thirteenth days following. The sixth dog resisted this inoculation and subsequently

showed itself refractory, owing to that same inoculation of January 23.

5. On July 13, 1886, seven new dogs receive under the skin of the abdomen two syringes each of the virus prepared from a rabbit belonging to the 118th passage of the rabbit series.

On the 20th of the same month one of them takes paralytic madness and lies down motionless, although still trying to bite a stick thrust at him.

The remaining six dogs resisted the infection. They were later on all six submitted to the test: subdural inoculation with the virus of ordinary dog madness. Four of them still remained refractory, an effect due to their first inoculation on July 13. The other two took paralytic rabies, but only thirty, twenty-seven, and twenty-eight days after their intra-cranial inoculation.

The case of the last two dogs shows that their inoculations of July 13 had not made them completely refractory; it shows also that they were partially vaccinated, if we remember that intra-cranial injection of the virus of ordinary dog rabies reproduces the disease in a much shorter time than twenty-seven and twenty-eight days. I am led to the belief that they were sufficiently well vacci-

nated to escape infection after bites of ordinary mad dogs.

6. On August 28, 1886, two new dogs receive under the skin of the abdomen ten syringes each of the virus prepared from a rabbit of the 122nd passage through rabbits. On the following days the two dogs give no signs of any discomfort. In order to know if they have been made refractory, they are trephined and inoculated subdurally with virus prepared from a rabbit just dead after infection from an ordinary mad dog. As a test experiment to verify the virulence of this virus, a new live rabbit is also inoculated with it at the same time as the two dogs. This control rabbit takes rabies on the sixteenth day after its inoculation, but the two dogs remain quite well and continue so for several months.

I could still give a very large number of such cases of acquired immunity after subcutaneous injections of any sort of rabies virus. It may seem strange that rabies is not produced, in certain cases, after such inoculations, if we consider that the quantities injected are relatively large, whilst an extremely small fraction of the same, if injected under the dura-mater, never fails to give rise to the disease. But what is much more surprising is the

production, in many cases, of an absolutely refractory state, and that without the previous appearance of any morbid phenomenon at all. Is not this last fact better explained by the action of some sort of vaccinal matter accompanying the rabies-microbe rather than by the action of the microbe itself? It is true that the refractory state is not brought on in every case, but it is easy to understand that, for many reasons, the vaccinal matter, granting its existence, will not under all circumstances be able to produce its effects before the microbe has fixed itself in some point of the organism favourable to its development.

How, again, can we understand, except by admitting the existence of a vaccinal matter, the last experiment cited—namely, two dogs receiving under the skin ten syringes each of the very virulent virus of the 122nd passage through rabbits, and at once rendered refractory to rabies? The large quantity of rabies microbes introduced under the skin must have reached the nervous system, and developed here and there in it, unless there was also injected at the same time some substance capable of travelling more quickly to that same nervous system, which it places in such a condition that the microbe can no longer be cultivated in it. It is easy to see, too,

that such experiments will not always be successful, but that rabies will often declare itself. For we must grant that in many cases the microbes will be able to fix themselves in some point which had not yet been preserved by the vaccinal matter.

It might be asked why intra-cranial inoculation invariably produces rabies and never the refractory state. It would not be a sufficient answer to say that by that process the virus is in all cases brought at once in immediate contact with the encephalon. For, as a matter of fact, the massive hypodermic inoculations must in a large number of cases have, quite as directly as by the intra-cranial inoculation, conveyed the virus and its figured elements to the encephalon by the venous or lymphatic channels. The real difference between the two modes of inoculation appears to me to consist in this circumstance, that subdural inoculation never introduces into the system more than a very minute quantity of virus, and, therefore, also of vaccinal matter, not enough to produce the refractory state, whereas for hypodermic injections the quantities used have always been much more considerable.

Dogs bitten by mad dogs do not always take rabies. That is a well-known fact. Such bites, like the subdural inoculation, can only introduce

into the system very small quantities of virus and of vaccinal matter. I have often made experiments for the purpose of ascertaining whether such bitten dogs which had not taken rabies had all the same become refractory to the disease: in every one of the cases tried the animal developed rabies when inoculated on the brain with the virus of an ordinary mad dog.

I have also made a large number of experiments with the object of seeing whether rabies was not oftener produced after hypodermic injection of relatively small than of larger quantities of rabid medullas of rabbits belonging to a series of passages. The comparison was made, as a rule, between inoculations of one-fourth, one, two, and ten Pravaz syringes. The general showing of the experiments has often been: 1, that rabies appeared to declare itself oftener after injection of one-fourth of a syringe than of one or several syringes; 2, that in those cases where rabies was not produced, the refractory state was oftener brought on by the use of large than of small quantities.

The following experiment would decisively demonstrate the existence of a vaccinal substance in the spinal marrows of rabbits which had died of rabies. One would have to prepare a set of mar-

rows, by desiccation, which should be absolutely non-virulent, and yet capable still, when inoculated into dogs, guinea-pigs, and rabbits, of rendering them refractory to rabies. This could be realised on the assumption that the microbe lost all virulence before the vaccinal matter did its power of prophylaxis.

A considerable number of experiments have already been made in that direction. Several of them did not lead to any very definite conclusions; in several cases the marrows experimented on were still slightly virulent. In others the inoculation of marrows which had lost all virulence failed to give the desired result—namely, the refractory condition of the animals inoculated with them. But on several occasions, also, I obtained sets of marrows, any one of which could be inoculated into rabbits after trephining without giving rise to rabies, even after intervals of two and three months; and yet those same marrows when inoculated into dogs and guinea-pigs rendered them refractory.

I have since renewed those experiments, and tried new sets of marrows, but have not this time been successful; and, being now far from my first successful results, doubts have arisen in my mind as to the accuracy of certain of my experiments

which I had considered as unimpeachable, and I have resolved to begin them again whenever I shall have the leisure. They are experiments of long duration, which might well be repeated by certain managers of stations for rabies-vaccination, better than myself, perhaps, able to devote to them the necessary time. Success in these experiments must consist in the use of marrows dried at a temperature as near as possible to the one which does away with all virulence in the rabies microbe. If after suspension in dry air at a temperature of 25° C. (77° F.) our marrows are found to have lost all virulence, they are the proper ones to use, beginning the inoculations with those even of six, seven, and eight days' desiccation.

The interest of possible vaccination by means of non-virulent marrows is self-evident, and need hardly be pointed out. It would both constitute a first-rate scientific fact and a priceless improvement on the present method of prophylaxis of rabies.

I should like, before closing this already long letter, to speak of a last point of great importance.

Certain facts indicated in my note of October 26, 1885, and also the cases of dog-inoculations which I have related in the course of the present letter, give us some idea of the profound changes

wrought in the properties of the virus of ordinary canine madness by successive transfers a large number of times through rabbits. Those changes are evidenced in various ways; thus we may consider only the duration of incubation in the rabbits successively inoculated. At the beginning, after a first passage from the ordinary mad dog to the rabbit, the average incubation is fifteen days. For this first passage into the rabbit, from any race of dog, provided only the animal has died of ordinary canine madness, I have never seen the incubation go below eleven days, and incubations of eleven and of twelve days are altogether exceptional: but after a large number of such passages have been made from rabbit to rabbit, the incubation goes down to eleven days, then to ten, nine, and eight days in succession, remaining long enough at the last period. Long before reaching the 80th or the 100th passage, the incubation has already lowered to seven days, without ever, even as an exception, going back to eight days. It remains a long time at seven days, only going down occasionally to six days. It is still seven days at the present time after the 133rd passage. Can we, then, conclude that in this direction, at any rate, the virus of rabies has come to a fixed point? Or

will the duration of incubation go down permanently to six days when the succeeding passages have reached far enough, in our races of rabbits, at least? Experience alone can decide the question.

The further we go from the initial virus of a series, and from the first serial rabbits, the less does the virus, hypodermically inoculated, become capable of reproducing the disease, especially so if large quantities are injected, whilst still, all the same, procuring the refractory state, as I have shown previously.

Finally, my dear Duclaux, I may add a few words on the duration of the immunity conferred to our vaccinated dogs. As you are aware, I have at Villeneuve-l'Etang a large kennel, where I have kept for two years now a considerable number of dogs which I had rendered refractory to rabies. At the end of their first year I tried on a group of them the criterion inoculation by trephining and injecting the ordinary street dog virus. Eleven of them out of fourteen resisted. This year again I tried the same experiment on six more which had been vaccinated two years previously: four out of six came out immune, and one of the two which did take rabies must have been partially vaccinated still, for it presented an incubation of twenty-eight

days; for the second one the incubation was twenty-one days. Both might, perhaps, have received with impunity the bites of ordinary mad dogs. With regard to the four refractory ones, the point is undoubted, as we know.

Postscriptum.—I think it will be useful to add in a postscript the following lines which I copy from a note which was recently given to me in Paris by Mr. Helmann, the present manager of the laboratory created in St. Petersburg for the treatment of rabies by the enlightened zeal of Prince Alexander of Oldenburg.

'Thanks to the initiative of H.I.H. Prince Oldenburg,' says Mr. Helmann, 'our operations on rabies were begun in the month of November 1885 with virus taken from a mad dog which had bitten an officer, who had himself been sent to M. Pasteur in Paris, there to undergo the preventive inoculations. With the same virus I inoculated three rabbits; two of them took furious rabies, which was again the form reproduced when new rabbits were inoculated from the first ones. It was impossible to obtain a case of paralytic rabies, whether by intra-cranial or subcutaneous inoculation, with a small or with a large quantity of virus, whatever also the race or the sex of the rabbits, whether the virus was taken from the medulla oblongata or spinal marrow.

'After the twelfth passage, however, there was occasionally now and then a case of paralytic rabies, and from the twentieth passage onward, one-half of the rabbits took the paralytic form; but it was found im-

possible from one of those paralytic rabbits to reproduce the furious form in rabbits. At the present moment I have reached the twenty-fifth passage, and the incubation is from eight to eleven days, varying with the quantity of virus inoculated. I had, as an exception, a case of prolonged incubation. A rabbit which had been inoculated on the brain on February 21, only took furious rabies on June 7 following.[1] A second one, inoculated on March 3, subcutaneously, fell ill on September 16. . . .'

The following description of furious rabies in the rabbit is very graphic, and applies generally even to our own varieties of rabbits:

'The symptoms of furious rabies,' says Mr. Helmann, 'are sufficiently characteristic. At the beginning the rabbit hides itself, and its ears begin to tremble; soon after it begins to plough the floor with its fore-paws and dashes itself about with so much violence that it often bruises its nose and forehead. After the period of excitement is over there comes on a stage of reaction, during which the animal remains motionless. If worried it will still make a few jumps, but soon go back again into its torpid rest, more especially so if the disease is near drawing to a close. When the excitement and agitation are at their highest, certain rabbits occasionally shriek. Paralysis sometimes supervenes before death, but never lasts more than a few hours. . . .

[1] If this inoculation, after trephining, gave this long incubation of three months and a half, it must have been owing to the fact that an extremely small quantity of virus only was deposited on the surface of the brain.

'Several rabbits which were inoculated after trephining in March last, with viruses dried at 35° C. (95° F.) for twenty-four hours, are still to-day in excellent health. At 35° C. the virus loses all virulence in twenty-four hours.

'In March also I inoculated four dogs with virus dried at 35° C. In June they were re-inoculated with virus dried at 23° C. (73·4° F.) Then again they received marrows of ten, nine, eight, seven, six, five, four, three, two, one day's desiccation. On July 31, two of the dogs were trephined and inoculated on the brain with fresh virus taken from an ordinary mad dog. The four dogs are still now in perfect health, and I consider them as refractory.

'In June 1886, H.I.H. Prince Alexander of Oldenburg brought back from M. Pasteur's laboratory two rabbits, belonging to the 116th and 117th passages. We at once set to work with the virus prepared from those two rabbits.

'On July 13, 1886, in presence of Messrs. Perdrix and Loir, the preventive inoculations in the human subject were begun, and on November 8 following, 118 bitten persons had already been inoculated. Out of that number one only, an old man over seventy years of age, died, after he had been submitted to the ordinary treatment inclusive of the third day marrow. He had received numerous and deep bites on both hands, and the period of incubation was very short, twenty days only.

'One hundred and thirteen of those 118 persons had been bitten by dogs, five by cats. . . .

'In order to ascertain whether the animals which had bitten our patients were really mad, inoculation experiments were performed on rabbits and on guinea-pigs. Out of forty-five dogs and five cats brought to the laboratory, some alive, some dead, forty-three dogs and two cats were found to be rabid, as verified by the successful intra-cranial inoculation of the virus taken from them into rabbits and guinea-pigs.'

The next three pages are given in a foot-note to the same article:

Many Russians had come to Paris for treatment who had been bitten by mad wolves or by mad dogs. I had thus had an opportunity in their cases of seeing how desperate such bites often are in Russia, and how short their incubation. I had accordingly written to Dr. Gamaleia, advising him, as an exception, to give all the inoculations in twenty-four hours. The following experiments justified me in giving such an advice:

On each of the following days, August 10, 12, 14, and 20, 1886, two new dogs were vaccinated, each animal receiving the whole set of marrows in the course of twenty-four hours. Thus:

On August 10 at 8 A.M. an inoculation under the skin of the abdomen of a full syringe of the fourteen days old marrow, diluted in sterilised broth.

On the same date—

At 10 A.M.	a syringeful	of the	12	days	old marrow
,, 12 A.M.	,,	,,	10	,,	,,
,, 2 P.M.	,,	,,	8	,,	,,
,, 4 P.M.	,,	,,	6	,,	,,
,, 6 P.M.	,,	,,	4	,,	,,

Rapid inoculation. [illegible] of 18 hours

On August 11—

At 8 A.M. a syringeful of the 2 days old marrow
,, 10 A.M. ,, ,, 0 ,, ,, (i.e. a fresh marrow.)

On August 12 same series repeated on two new dogs—namely, inoculations with the marrows from 14 to 0 days old, every two hours, at 8 A.M., 10 A.M., 12 A.M., and 2 P.M., 4 P.M., and 6 P.M.; and on August 13, at 8 and 10 A.M. with the marrows of 2 days and 0 days.

On August 14, repetition of same experiment on two new dogs with marrows from 14 to 0 days, every two hours, except the two last, which were given in the forenoon on August 15.

On August 20, finally, same series tried on two new dogs in identical conditions, and ending therefore on the 21st in the forenoon.

We thus had four series of two dogs each, which had all received the whole set of marrows from 14 to 0 days in the space of eighteen hours only.

The eight dogs were soon after tested as to their refractoriness to rabies, the two first ones as early as August 12, thirty hours only after their last inoculation: those of August 12, 14, and 20, were tried on August 25, after thirteen, eleven, and five days. Therefore, the test experiment consisted, for every one of them, in an inoculation on the surface of the brain, after trephining, of the virus taken from an ordinary street mad dog.

Four only of those mad dogs died of rabies, one of the four belonging to the set of August 12 taking the furious and biting form of rabies. Of the other three, one belonged to the set of August 10, the last two

were the two dogs of August 14; the two animals of August 20 remained well.

I ought to say that the second dog of August 10 became very weak in the hind quarters on the 28th and 29th of the same month, but he finally recovered from those first symptoms of paralysis, and by September 6 ate well and was all right again. Its fellow of August 10 was very agitated and weak in the hind quarters as early as August 26, neither barking nor prone to bite. It died completely paralysed on the 30th of the month.

It is probable that a second and perhaps a third set of vaccinations would have rendered all the eight dogs refractory. In any case, even that partial success, four dogs out of eight made proof against rabies by a set of vaccinations effected in eighteen hours only, demonstrates that, notwithstanding the rapidity of its application, the method is capable of very great efficiency.

Another demonstration that the inoculations are capable of rendering dogs rabies-proof in a short space of time is furnished by another kind of experiment, in which we invert the order of the two operations and inoculate the infective virus on the brain before we vaccinate.

On September 8, 1886, four new dogs are trephined and inoculated on the brain with the bulb of a dog which had recently died of rabies, and which had itself been inoculated from an ordinary street mad dog.

On the following day, Septemper 9, they received under the skin a full syringe of the marrows of fourteen, twelve, ten, eight, six, four, and two days; on the 10th

they received the marrows of two and 0 days, at eight and at ten o'clock in the morning.

Two of those four dogs became mad on the fourteenth and on the twenty-ninth days after they had been trephined; the second one had, therefore, been at least partially vaccinated. The other two remained perfectly refractory.

We may note in passing that it would be difficult to find more convincing proof of the possibility of rendering dogs refractory to rabies, and by extension man himself, than that afforded by the details we have just given concerning those twelve dogs; it is well in that connection to remember that intra-cranial inoculation of the virus of rabies reproduces the disease in animals with the utmost constancy.

. . . . . .

There are no bites which, in point of gravity, can be compared with intra-cranial inoculation after trephining.

CHAPTER III.

TECHNIQUE OF THE METHOD.

We shall now proceed to give an account of the technique of the method of preventing rabies after bites. We give it from what we have seen ourself and as applied at the present day.

The Mad Dog and the Mad Rabbit.

Suppose a mad dog which has either been killed or which has died of the disease itself. We shall start from it in the preparation of our rabbits and then of our prophylactic viruses.

The first thing is to take out the brain and the medulla oblongata of the animal, as cleanly as possible. Lay them on a clean plate, with the basal surface upwards. Whatever parts have to be touched or handled should first be wrapped up in paper. The nervous matter ought only to be handled with the help of flamed sterilised instruments: dissecting forceps, scalpels, curved-bladed

scissors. The free end of the medulla is grasped with the forceps and thrown over towards the frontal lobes, whilst all adhesions to neighbouring parts are divided with the scissors. The fourth ventricle is now opened up and exposed to view. From the central part of its floor, i.e. from the medulla oblongata portion of it, is cut away a piece about the size of a small pea, and usually also another small fragment from the neighbourhood of the central

Fig. 1.—Glass for preparing the Injection-fluid.

canal, the medulla having by this time been completely detached from the brain. The two small segments of nervous matter are put into a small conical glass, about half an ounce in capacity, and from which the filter-paper cover is only removed at the time (fig. 1). Glass and paper cover come from a stove where they have been sterilised by exposure for a quarter of an hour or more to a temperature of 120° C. (248° F.). The little pieces of nervous matter are triturated in the glass by means of a stout

glass rod which has also been well flamed. When all reduced into a fine jelly-like mass, sterilised veal-broth is added, at first drop by drop and then more freely, stirring all the while until it makes up a turbid thick liquid amounting in quantity to about half a table-spoonful. The paper cover is laid on again and the glass put by ready for further use.

All the instruments are well heated in a flame after the operation is completed, just as they were at the beginning, but this time solely for the purpose of destroying any rabid matter on them and guarding against accidents to servants or others.

We may now pause a moment and consider a few accessory points before proceeding further.

The expression 'to sterilise' may not be quite familiar to the casual reader. It is a term of bacteriology, the science of bacteria, micro-organisms, germs, or microbes, and describes the operation by means of which we destroy all living germs in or upon an object or substance, generally deposited from the air, where they float as dust. There are many sterilising agents; thus, to name a few only, sunlight, oxygen, desiccation, heat, dry or moist, so-called antiseptic substances, such as the bichloride of mercury, carbolic acid, quinine, &c.

Those of the instruments which come in contact

with the portions of nervous matter actually used are sterilised by holding them for a few moments in the flame of a gas-burner or of a spirit-lamp and then allowed to cool down for a few seconds before they are used. This is the quickest and most efficient method of sterilisation, also preferable to all others in the present instance because it does not add any adherent antiseptic or sterilising substance to our nervous matter, which it is our only aim, so far, to keep perfectly pure from any admixture. Atmospheric or other germs, if they gained access into our medulla and broth would, when injected under the skin of an animal or of a man, as the case might be, give rise to various accidents, local or general, inflammation, suppuration, gangrene, and even septicæmia. The action of the rabid poison might thus at the same time be perverted or even nullified.

The broth is prepared as follows: Take equal weights of lean veal and of water, two pounds of veal and one litre (thirty-two ounces) of water, and a glassful more to make up for evaporation. Remove all fat, bone, tendon, loose connective tissue, &c., from the veal and cut it up into small pieces. Put these in a clean vessel with the water, cold, and leave soaking for two hours. Then put

the vessel on a slow fire and keep stirring until it just begins to boil. Remove from the fire, neutralise, if need be, with a little potash, filter through ordinary filter-paper and distribute into a number of small flasks (fig. 2), each containing about three ounces.

As seen in the figure, the flask has two apertures. The lower one is sealed with the blowpipe;

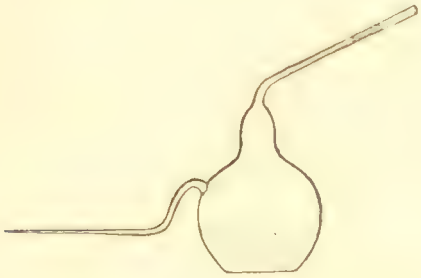

FIG. 2.—Balloon-pipette for keeping the Sterilised Broth.

the broth is poured in through the upper one, which is then closed with a plug of cotton-wool. As is well known, cotton-wool allows air to filter freely through its meshes, but efficiently stops all dust suspended in it.

The flasks are now put into an autoclave or stove at a temperature of 120° C. (248° F.). All germs are killed at that temperature, and in a quarter of an hour the flasks may be taken out and

stowed away on shelves; they are sterilised, i.e. will keep pure for any length of time. At the Pasteur Institute the broth is prepared once a fortnight, ten litres at a time, and serves both for the rabies and for the splenic fever departments. The same man who prepares it is the glass-blower of

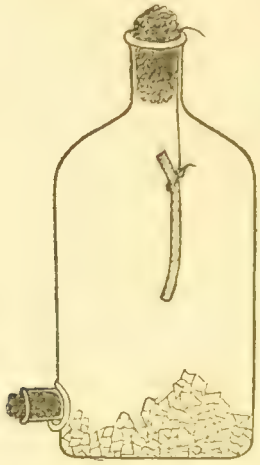

Fig. 3.—Drying Bottle and Marrow.

the establishment and blows most of the glass apparatus used.

The bottles in which the spinal marrows are desiccated are of the capacity of one litre (fig. 3). The two apertures are closed with cotton-wool pellets, and the whole put for twenty minutes in a stove at a temperature of 120° C. It is then taken out sterilised and the cotton all brown. The top plug

is removed and a handful of solid caustic potash, broken up into fragments, thrown in, filling the bottle as high as the level of the lower aperture. The plug is put back, and the bottle is ready to receive the marrow. The same bottle can be used twice, and then the potash is thrown away and a new supply of it put in, after renewed cleaning and sterilising of the vessel. It may perhaps be worth while to remark that there is a free circulation of air in the bottle through the two cotton plugs, but the air which thus circulates is filtered, deprived of all dust and germs by the cotton-wool, as also of moisture by the hygrometric caustic potash. When, therefore, it comes in contact with the piece of fresh moist spinal marrow suspended inside the bottle, it borrows moisture from it, a moisture which it parts with in favour of the caustic potash if the current of air be from above downwards, which is lost in the general atmosphere of the room if the current be from below upwards.

The bottles are labelled, mentioning the number of the passage of the rabbit whose spinal cord is drying (beginning to count from the first rabbit inoculated from the dog), and also the date of bottling. The bottles are then arranged in order on a table in a small dark room kept at a constant temperature

ranging from 20° to 25° C. (68° to 77° F.). This room is never swept, the windows are never opened, the door just gaped to let in the person who prepares the viruses for human inoculations, and nobody but him ought ever to go into it. All those precautions aim at keeping the air of the room as undisturbed as possible, so that the germs floating in it will be as few as possible, and therefore the danger of their falling into the small glasses during manipulation at the lowest.

The hypodermic syringes used for the inoculations are the ordinary Pravaz syringes, containing one gramme of liquid when full (one cubic centimètre). They are to be kept scrupulously clean and efficient. Whenever a set of inoculations is over, morning or evening, the syringe is broken up into its constituent parts. All the soft parts, the leather, is thrown into the fire and destroyed. The metal parts are dropped into boiling water and left in it for a few minutes, for the purpose of destroying all adherent virus (the syringes are made of silver), after which the needles are sent to the instrument maker, who sharpens them anew and polishes them. He also renews the soft parts, which are constantly kept soaking in aseptic oil. The oiled leather does not imbibe the aqueous virus.

By means of all those little precautions the virus is inoculated as pure as possible, and the prick of the needle is made with the minimum of pain to the patient.

The inoculated rabbits are kept two together in cages made of strong iron-wire netting with abundance of straw for their litter. The litter is changed every day. They are fed on a mixture composed of two parts bran, one part oats, one part corn, and one part buck-wheat, three handfuls a day for each cage, i.e. for two rabbits; also one carrot or one or two leaves of lettuce per cage. Nothing more, no water. With this régime diarrhœa is avoided and the animals are kept in good health until the symptoms of rabies show themselves, somewhere between the fourteenth and twentieth days probably, in rabbits of the first passages, death occurring in three, four, or five days; some animals, the stronger ones, resisting longer than others. Rabies always assumes the paralytic form in the rabbit, except in the first few passages from the dog, when it is often furious. The hind legs become paralysed, and the animal crawls about in its cage, dragging them, or oftener sits or lies down motionless. Gradually the paralysis ascends and the fore legs are also implicated, and the animal lies down quite helpless,

except the jaws, which still occasionally stretch right and left in search of food. It is now necessary to look after the animal with especial care, as otherwise vermin will often attack it and interfere with the progress of the operation. Death ultimately takes place by implication of the nerves of respiration and asphyxia.

The main naked eye post-mortem appearances are shortly dealt with, for they are summed up in one word: congestion of the nervous centres, and in particular of the medulla oblongata, where at times it goes so far as to give rise to hæmorrhage by rupture of small vessels. Congestion of the lungs is not unfrequent, especially in the furious forms of rabies. Those post-mortem appearances are evidently not pathognomonic of rabies, and may be met with after death from various other causes.

Gentlemen wishing to work at rabies or to apply the prophylactic treatment at home have only to bring a couple of rabbits to the laboratory and get them inoculated. If going long distances, say to South America, it will be necessary to keep in readiness a few more live rabbits, which can in turn be inoculated on the way with the medullas of the first ones, which will die on the eleventh day or thereabout after inoculation. In this fashion it becomes

possible to have abroad a series of inoculated rabbits identical with the mother series kept at the Pasteur Institute in Paris. If travelling shorter distances, it will be enough to take with one portions of a rabid medulla and cord kept in ice, carbonic acid or glycerine at 30°. The last-named substance preserves the nervous matter with its virulence intact for a whole month. The glycerine ought to be neutral and quite pure (Roux).

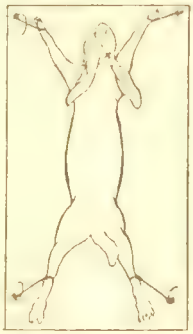

FIG. 4. The little star shows the place for the Trephine.

We now go back to our dog-virus which we left diluted in veal-broth and all ready for further use. The next step consists in inoculating it into a rabbit, on the surface of the brain. The animal, full-grown, alive and healthy, is placed upon a plank, flat on its abdomen, and its four limbs stretched out and secured by strings to pegs driven in the wood (fig. 4). A double sheet of filter-paper is folded roughly into the shape of a funnel, a teaspoonful or less of chloroform poured into it, and the whole stuck firmly over the nose and mouth of the animal. It wriggles a little, and in one minute is fast asleep. The assistant holds

the head steady whilst the operator cuts the hair covering that part short and makes along the median line an incision one inch long and running backward from a point midway between the two eyes. He cuts down to the bone and inserts an ordinary eye-dilator or blepharostat, to keep the lips of the wound gaping. This also he entrusts to his assistant whilst he himself proceeds with the delicate operation of trephining. He uses a small trephine, with a crown about one-sixth of an inch in diameter, and such as is employed in aural surgery for trephining the mastoid cells (fig. 5). He applies it in the median line, a quarter of an inch or so behind the line joining the two eyes. He works very gently, taking care to cut nothing but bone and not to injure the underlying meninges. The circular piece of bone trephined is removed by means

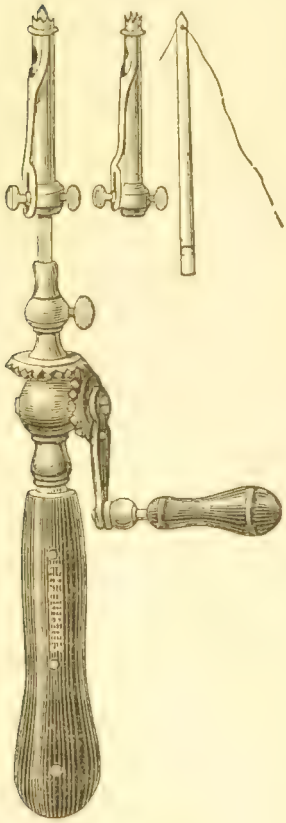

Fig. 5.

of a strong curved needle, and the cerebral membranes come into view. He now takes a hypodermic syringe with curved needle and so constructed as to allow one to count the number of drops injected. This is filled with the dog-virus contained in the small conical glass; the point of the needle is inserted under the cerebral membranes and two drops of the virus injected. When the needle is removed a small quantity of cerebro-spinal fluid sometimes regurgitates through the little aperture in the dura-mater, but there is no harm in that. The wound is bathed freely with a three per cent. solution of carbolic acid and the skin flaps sewn together by means of two or three sutures. The whole operation has only lasted three minutes. The rabbit is by this time out of chloroform, but still dulled. Soon, however, it regains consciousness and begins to eat as if nothing were the matter. The operation is constantly successful, the wound is healed in two days, and not more than one or two per cent. of the animals die under chloroform. If larger animals, such as dogs, are trepanned for purposes of inoculation, it is well to apply the instrument some distance right or left of the median line, not on it, in order to avoid wounding the longitudinal venous sinus and giving rise to

very troublesome and sometimes fatal hæmorrhage. In rabbits the loss of blood is practically *nil*. It goes without saying that at the same sitting several rabbits may be inoculated.

From this first batch of rabbits we select the one which dies first and operate as early after death as possible, in order to have it quite fresh. Proceed as in the case of the dog, extract the medulla and brain, and from the former prepare another small glass of virulent broth. This, as before, inject under the cerebral meninges of a few more fresh live rabbits. They will take the disease after a shorter time of incubation. Proceed again with the first ones that die to inoculate fresh animals, and so on until at last we come to a period of incubation of seven days' duration. As we know already, this is about the shortest incubation attainable, for, after more than a hundred and fifty such passages or transfers through rabbits, it still remains seven days, or occasionally an hour or two less. The incubation of seven days' duration is already reached by the fiftieth passage. The rabbit taking ill on the seventh day and dying on the tenth day or later is the one used for human inoculations as well as for the purpose of perpetuating the disease in other rabbits. By dealing with

a sufficiently large number of animals it is possible to have a rabbit dying every day, and thus also to put one spinal cord in a drying bottle every day. We shall, therefore, by the fourteenth day have a set of fourteen marrows undergoing the desiccation process, and be in a position to begin our prophylactic inoculations. If beginning work abroad, the set of fourteen spinal marrows will be more quickly obtained by daily taking out and bottling a small piece of a spinal cord preserved in carbonic acid or otherwise, and it is well in such circumstances to try a few test experiments on dogs, rabbits, or guinea-pigs before launching out into the treatment of human subjects.

The spinal marrows of more than fourteen days are thrown away as being inert and useless. At the Pasteur Institute there are two rabbits inoculated, and therefore also two dying (of rabies) every day, for fear if one alone were used it might die from accident and the series be interrupted. Practically one animal is found to be quite sufficient, and the second one is only inoculated for prudence' sake.

The medulla or cord of a rabbit in which the incubation has been seven days, when injected intracranially into a dog, develops rabies in the latter animal in about twelve days. The nervous matter

of this dog, inoculated back by the same process into rabbits, at once reproduces the malady after an incubation of seven days, and thus the series is recovered. On this experiment is based the test-method for ascertaining whether a person has died of inoculated rabies or not. Portions of his medulla are diluted in broth and injected intra-cranially into a number of rabbits. If the person died of rabies communicated to him by the Pastorian virus the rabbit ought to develop the disease on the seventh day after inoculation and to die somewhere about the tenth or eleventh day.

The rabbits commonly used in Paris are, on the average, five or six months old, weigh two kilogrammes and a half (5 lbs.), and measure from 45 to 50 centimètres from tip of nose to root of tail. These details are worth noting, for it has been found that smaller or younger rabbits take the disease quicker and also die quicker after its onset. A lean weakly animal will also die quicker than a strong fat one of the same age.

In Russia rabbits are generally much smaller than in France, and therefore react in a way slightly different, taking ill and dying at earlier dates after inoculation.

As we have already seen in the 'communications,' the virus of an ordinary mad dog or of a

mad rabbit injected directly into the veins of a dog generally gives rise to paralytic rabies. The same virus injected upon his brain produces furious rabies. Pure water, simple sterilised broth, or the same containing a quantity of pulverised marrow of fourteen days' desiccation, the blood, the urine, of a rabid animal, injected on the brain of dog or rabbit, do not give rise to rabies. Such has been the result, at any rate in a large number of experiments. There was only one exception in favour of the blood, and the fourteenth day marrow, if injected in very large quantities, does exceptionally reproduce the disease.

The bodies and all the unused parts of dead rabid animals are put in a large tub containing a four per cent. solution of sulphate of copper. Once a week the knacker comes round and carts them away. He plunges his bare arms in the liquid and deals with the carcases just as if they were common non-rabid ones. Their virulence is all destroyed.[1]

Several guinea-pigs have been inoculated and rendered refractory, and then allowed to produce young ones for the purpose of ascertaining whether their acquired immunity is hereditarily transmitted

[1] Of all sterilising agents, it would seem that turpentine is the one which possesses the greatest activity—*in vitro*—against the specific virus of hydrophobia.

to their young. But these experiments, like many other subsidiary ones, are not yet completed. The main objection to the use of guinea-pigs in the preparation of the prophylactic virus is the small size and fragility of their spinal cord, which renders them very inconvenient practically. Occasionally a rabbit or a dog is hit upon which presents a longer period of incubation than it ought to from the strength of the virus used. Such cases remind one forcibly of analogous ones of protracted incubation in man after bites. The virus or seed is the same, but the patient or soil varies, is more or less fertile, and offers greater or less resistance.

The Marrow. The Vaccinal Virus.

The dead rabbit is taken up soon after death, when still quite fresh, and laid flat on the abdomen. It ought, like all rabid material, to be handled with the greatest care, and any part touched with the fingers ought to be wrapped in paper. The workers at the Pasteur Institute have, several of them, been vaccinated as a safeguard against accidental infection from the animals they manipulate daily: so also about twenty sound persons working in different branch-institutes, in Russia in particular. There never followed any untoward effects. The

assistant holds the cadaver steady, and the operator proceeds to slit up the skin along the dorsal median line, from the head down to a few inches from the root of the tail. It is thrown back freely right and left, and then the muscles are detached from

Fig. 6.

Fig. 7.

the skull, the spine, and the ribs for half an inch or so on either side of the vertebral column. The spinal processes are cut away with the curved scissors and the skull cap broken off in fragments by means of Liston's bone-forceps (fig. 6), the left

hand all the while holding the muzzle firmly gripped in Farabeuf's davier or crab-claw forceps (fig. 7). When the brain and medulla have been sufficiently bared, slit up the meninges covering them and remove those two parts, which place in a clean dish with their basal surface upwards. Then, still using the same instruments, proceed to remove the vertebral laminæ with the roots of the spinal processes covering the spinal cord. Cut them right and left alternately, from above downwards, inserting the point of the blade of the bone-forceps into the spinal cavity, between the spinal meninges and the laminæ, and taking great care not to tear the former and injure the cord. It requires a certain amount of practice to bare and extract the cord intact, in particular from the narrower parts in the neck and shoulder. It is sufficient, as a rule, to expose the spinal cord for a distance of about eight or ten inches. Then divide it transversely with the scalpel, seize the lower extremity of the exposed portion with the dissecting forceps, and raise it from the spinal groove where it is lying. Successively cut all the spinal nerves which hold it down, and work up towards the head. In that way remove the cord, with its membranes, and place it in another clean dish. Cut it into segments about

three inches long, and tie a thread to one end of each of them. Now take a drying-bottle and insert into it one of the segments, which hold hanging by means of the thread. Whilst introducing it into the bottle take care that it does not touch the sides of the neck, and when it has got fairly in, about the centre of the vessel, put back the cotton-wool stopper so as to catch the free ends of the thread between it and the neck of the bottle; the piece of spinal marrow will thus be kept hanging vertically over the bed of caustic potash, in the centre of the bottle. Proceed similarly with the other pieces of marrow, if more than one should be judged necessary. From them will be by-and-by prepared the vaccinal viruses. At the Pasteur Institute two such 3-inch segments daily are found to be quite sufficient for all purposes. Label the bottle, mentioning the number of the passage to which the rabbit belonged, and also the date of bottling. Next put them away and keep them at a temperature ranging between 20° and 25° C., as previously mentioned.

The bulb or swelled-out topmost portion of the medulla oblongata of this same rabbit is used at once for intra-cranial inoculation into two fresh live rabbits, for the purpose of perpetuating the disease and the series. The remaining portions of the

animal are thrown away into the solution of sulphate of copper.

This marrow we have just bottled could at a stretch serve on the same day or on the next, for the last inoculation, the most virulent, of a patient finishing his treatment. On the fourteenth day the same marrow, having its virulence reduced to its minimum owing to desiccation, will serve for the first inoculation of a patient just beginning treatment.

The same process is repeated every day, so that, to sum up, we have daily two dead rabbits (only one of which is actually used), two pieces of spinal marrow bottled, two fresh rabbits inoculated.

We thus have, at any time after the fourteenth day, two sets of marrows drying, going from those of the fourteenth day up to and including those of the first day, the latter being the most virulent and the former the least so. If we only bottled one segment of marrow, we only have one such set; if three, three, all three identical. On drying, the marrows become crumpled up and brittle; grey-white and streaked red by the blood-vessels when fresh, they gradually darken in colour and are uniformly dark-brown by the fourteenth day, owing apparently to the blood which was contained in their substance oozing to the surface, where it dries up. The super-

ficial parts of the piece of marrow are naturally sooner dried and at any time drier than the more central parts surrounding the central canal.

The attenuated and graduated viruses for human inoculation are prepared in exactly the same way that we prepared the medulla of the dog for inoculation into our first rabbits, only now we use the desiccated spinal cord instead of the fresh medulla oblongata. The reason for the preference given in this instance to the spinal cord is that it is more easily managed owing to its regular and convenient shape. The virulence is the same in the two.

The quantity of marrow used for human inoculations is about one millimètre for each person, judging approximately, with the naked eye. Suppose ten persons applying for treatment to-day, i.e. being on the first day of their treatment, ten millimètres of the marrow which has been in the drying bottle for fourteen days are cut with flamed scissors and dropped into a sterilised conical glass just come from the stove, and from which the cover is only removed at the time. It is next reduced into as fine a powder as possible by trituration with a flamed glass rod. Then ten cubic centimètres of sterilised veal-broth is added, at first drop by drop and then more freely, stirring all the while. The broth is

taken from one of the flasks shown on page 131 by breaking off the tip of the lower nozzle and blowing through the upper or vertical aperture, through the cotton plugging it. The lower nozzle is then sealed with the blowpipe, and the remaining broth will still keep pure and can be used again and again.

The scissors and glass rod are again passed through the flame and laid aside, and the paper cover is put back and made to fit tightly on the conical glass, which is left standing for half an hour or so. In practice use two or three more millimètres of marrow and two or three more cubic centimètres of broth, because more patients may turn up at the last moment, and also because it is better to inject the clearer supernatant liquid than the lower strata, which are mixed up with the deposited larger and heavier particles of marrow. The virus is now a greyish fluid, cloudy and thick from the presence of a large number of fine molecules of marrow held in suspension ; it is not unlike rice water in appearance.

In the same manner the marrow of thirteen days' desiccation is prepared for those patients who are on the second day of their treatment, the marrow of twelve days' desiccation for those on the third day of their treatment, and so on.

As soon as the glasses are all ready they are labelled, mentioning (*a*) the age of the marrow, (*b*) the number of persons to be inoculated from the particular glass, as ascertained beforehand from the secretary. They are then arranged in order in a small wooden box and are ready for use.

The Inoculations.

These, the treatment proper, were at first carried out at M. Pasteur's small but historically interesting laboratory in the École Normale Supérieure, Rue d'Ulm. The patients soon became so numerous, however, that it became necessary to look for more spacious and convenient premises, and the main seat of the operations was transferred to No. 14 Rue Vauquelin. The Pasteur Institute proper will be erected later on, when the necessary funds have been collected, in Rue Dutot (Paris). The rabbits are still kept and inoculated at Rue d'Ulm, but all else belonging to rabies is done at Rue Vauquelin. Here also is prepared the vaccinal virus for splenic fever. A few mad dogs are kept at this place, but the great body of them is at Villeneuve l'Étang, a Government property in the neighbourhood of Paris, placed at the disposal of M. Pasteur

in addition to a considerable annual grant allowed him in aid of his researches and experiments.

The present building is essentially composed of four rooms. The largest one is the waiting-room for the patients, with a screen behind which the women can go and bare a square inch or so of their hypochondria beforehand. It opens into the office, where the secretary of the establishment keeps his books and takes down the names of the patients and all particulars concerning them. The office in turn communicates with the inoculation-room, the one where the inoculations are actually made. The fourth room is the surgery, communicating with the last two. Here the bites and wounds of the patients requiring dressing are attended to under the general supervision of M. Terrillon. As a rule they heal kindly under the ordinary treatment of common wounds; iodoform and carbolic acid are chiefly used.[1]

In the inoculation-room the interest centres round a small fenced-in area in the middle of the room. Within the area sits the vaccinator, Dr. Roux, one of the gentlemen who, in 1884, went to Egypt on the cholera-mission. By his side one or

[1] Quite recently iodol has been substituted for iodoform. It has the advantage of being odourless.

two medical gentlemen helping him. Close by, a small table entrusted to the care of M. Viala. On this table we find our small wooden box containing the complete series of our conical virus-glasses, prepared an hour ago, two or three hypodermic syringes, and a spirit-lamp on which is kept boiling a small tin pan full of water in which has been dissolved some chloride of calcium. This addition raises considerably the boiling-point of the liquid. Plunged in the water there is an ordinary test-tube filled with ordinary sweet oil, whose temperature is soon brought in this water-bath to close upon 100° C., the boiling-point of pure water. Lastly, a sheet of paper is communicated by the secretary with a list of all the persons to be treated at the particular sitting, arranged in groups according to the day of their treatment and the particular marrow or glass from which they are to be inoculated. This, along with the previous labelling of the glasses, as we have seen it done, ensures and facilitates control. We give below the copy of one of those lists :—

April 19; Eleven o'Clock.

—	persons	Marrow of April 5		Marrow aged 14 days			
3	,,	,,	,, 7	,,	,,	12	,,
3	,,	,,	,, 8	,,	,,	11	,,
7	,,	,,	,, 9	,,	,,	10	,,

4	persons	Marrow of	April 10	Marrow	aged	9	days
11	,,	,,	,, 11	,,	,,	8	,,
26	,,	,,	,, 12	,,	,,	7	,,
11	,,	,,	,, 13	,,	,,	6	,,
3	,,	,,	,, 14	,,	,,	5	,,

The first horizontal line refers to those persons who have just come and are receiving their first inoculation. Their number is only put down when they are, at the next sitting, receiving their second inoculation and forming the second group. The second line refers to persons receiving their third inoculation; the third line to those receiving their fourth inoculation; the ninth line to those receiving their tenth inoculation, and finishing the course of treatment. The marrow of April 4, fourteen days old, was inoculated in the morning of the 18th, i.e. on the preceding day, to the three persons in the second line; the marrow of April 5, thirteen days old, was inoculated into them on the evening of the same day. The marrow of twelve days, which they had to receive on the morning of April 19, was that of April 7; hence the absence on the list of the marrow dated April 6.

Thus we see that on April 19, at eleven o'clock A.M., there were *n* persons beginning treatment, and inoculated from the marrow which was bottled on April 5, and therefore had, on the 19th, been

drying fourteen days. This, as we know already, is the weakest virus used. Similarly, also, the three persons in the second line were receiving their third inoculation with the marrow of twelve days, and so on. Finally, the operation was ended at that same sitting with the last group of three persons who were receiving their tenth or last inoculation from the marrow bottled on April 14, and only five days old. This is the most virulent marrow used at the present time, in winter. In summer, during hot weather, other conditions remaining the same, it is found that the virulence of the marrows undergoing desiccation disappears more rapidly than in cold weather, and therefore the last inoculation is made with the marrow aged four days, which is the one corresponding in virulence with the winter marrow of five days.

The patients assemble in their general waiting-room every morning at ten o'clock—one hour before the time for the inoculations to begin. The secretary or his assistant then inscribes the names of all new-comers in a large register kept for the purpose, two pages for each person. The bites are examined, and if the skin is found to be unbroken, simply contused through the garments, or occasionally even less than that, the applicant is told

to go home and keep his mind quiet. He is in no danger. The patients who have been actually bitten are kept for treatment.

We shall now give the scheme according to which the patients are examined and inscribed.

The parts within brackets have been added by ourselves, and the different headings sufficiently explain themselves. Under 'Remarks' are noted particularly whether the patient is of alcoholic habits, of the neurotic disposition, subject to epileptic fits, syphilitic, &c. All the patients are inoculated with the same syringe, except the syphilitic ones, who have a special syringe put apart for them.

When the examination and inscription of new patients is over, they go back into the waiting-room, and the secretary or Dr. Charrin draws up a nominative list from his books of all the patients to be treated at the particular sitting, arranging them in groups according as they are to receive their first, second, third, or last inoculation. He also draws up the other list, which we have already noticed in the inoculation-room. The treatment can now begin. He stands in the office, near the door opening into the inoculation-room, and calls into the office all the new patients. Then he calls out loudly the date of the marrow to be used and

Name in full . . . . . .
Age and profession . . . . .
Address . . . . . .
Date of bite . . . . . .
Seat of bite . . . . . .
Number of bites . . . . . .
State of bite . . . . . .
Dress, torn or not . . . . .
Cauterisations : red iron . . .
Cauterisations : chemicals . .
Date of cauterisation . . . .

Veterinary Information
Name and address of V.S. . .
Certificate . . . . . .
Results of examination of animal before death . . .
Results of examination of animal after death . . . .
Additional information . .

Special Information
To whom does the animal belong? . . . . . .
What has become of it? . .
Changes in its voice . . . .
Changes in its temper . . .
Have other persons been bitten by it? . . . . .
Have other animals been bitten? . . . . . .

Laboratory Information
Dog brought on the (date) .
Post-mortem examination .
Inoculation experiments . .

TREATMENT

Number of the inoculations	Date of the inoculation	Hour	Dose	Date of the marrows (date of bottling)	Age of the marrows
			Syringe		

REMARKS

nominately those first patients one by one. They in succession walk into the treatment-room, bare their hypochondriac region, and receive from Dr. Roux a hypodermic injection—a full syringe for adult men, one-half or more for adult women, and only one-third of the syringe for children. The syringe is filled by M. Viala by thrusting its needle through the paper cover of the glass prepared from the fourteen days old marrow. The needle is then dipped into the hot oil and handed to the inoculator, who immediately after the operation returns it, to be filled and oiled anew. The inoculations are thus rendered as painless and as aseptic as it is practically possible to make them. The patients are now told when they are to come back, and walk away home or else pass into the surgery to have their wounds dressed if they require it.

When this first group is done the secretary calls out the date of the next younger marrow. On hearing this, M. Viala, who is also all the time keeping his eye on his own list and controlling the numbers, puts by the first glass and brings out the one prepared from the marrow thirteen days old, and proceeds as before. Meanwhile the secretary has called the second group—those going to receive

their second or third inoculation, as the case may be—into the office, and thence one by one they pass into the treatment-room. And so on for the different groups in order, up to the last, those inoculated from the five-day-old marrow.

The surplus of the different viruses is emptied into some safe place, the glasses carefully sterilised, the syringes unscrewed and broken up and treated in the way previously mentioned—and the morning sitting is over.

The order adopted for the inoculations is the safest for the patients themselves, and, further, permits of the use of a single syringe for them all. The injections are made first with the weakest virus and then progress upwards, ending with the strongest. Supposing some particles of a previous virus to have remained adherent to the needle, the next patient runs no danger from them; he has already received a full inoculation from that virus at the previous sitting, and is now actually receiving a stronger virus. Had the reverse order been adopted, and supposing the same accident to occur, the patient would be receiving into his system portions of a stronger virus than he was ready to receive, and might thus be exposed to some risk. To guard against that possible danger it would

then become necessary to use a new syringe for every group.

It would be difficult to see anywhere else, and within such a small space, a more curious or motley assemblage of people. They at the present time number close upon one hundred every morning, occasionally more. During the first months, and before the establishment of the branch-stations in Italy, Austria, Russia, and elsewhere, they often came up to two hundred, and the variety of people was even greater than it is now. The Russian soldiers and peasants and their solemn popes, the gaudily dressed Italians, were then conspicuous. But we still have lords and ladies from every latitude; peasants from all corners of France in their frequently picturesque attire; Spaniards and Bretons, with their broad-rimmed hats and tight-fitting dress, reminding one of the Eton boys of England; soldiers and sailors; Turks, Arabs, and negroes from Algeria and elsewhere, the latter wrapped up in their flowing white burnous: and in the midst of them all an abundant sprinkling of anxious but not dumb children. These often scream fearfully when their turn comes, but it is much more from fright than from pain. A copper or a biscuit in time saves many a scream. Ner-

vous ladies may receive their inoculation in a small side-room. Now and then a patient faints away, but the accident is trifling and never lasts more than a few minutes. They often inquire as to the regime to be followed during treatment or after it. There is none really, although for obvious reasons it is not unusual to hear the recommendation made, 'Be sober in all things —no alcoholic excesses.' As a matter of fact, it is found that, of those patients who succumb from rabies after the inoculative treatment, a large proportion belong to the class of alcoholic or neuropathic people, the hysterical and the epileptic. Those circumstances do not make the treatment counter-indicated, but ought to render the prognosis more guarded (Grancher).

The hypochondria (or certain abdominal regions) are selected for inoculation, because it is found that in those regions the subcutaneous cellular tissue is looser, more rapidly absorbent. There is occasionally a small area of redness round the point of inoculation, after the more virulent ones in particular; but it subsides spontaneously in a day or two. The alternate inoculations on the right and the left sides further facilitate the subsidence. If need be, the patient is told to rest for a day or two and take a

hot bath. This treatment is uniformly sufficient to rid the patient of the small inflammation and to allow him to proceed with his treatment. Only in one instance, out of many hundred cases we have witnessed, was there some considerable swelling and pain in the axillary region. The same simple treatment soon put matters right.

We may now dwell with some detail on a few points of paramount importance. Suppose a patient—*ab uno disce omnes*—turning up who has been bitten on the leg, through his clothes. He receives a first inoculation with the fourteen-day-old marrow. Next day he receives the thirteen-day-old marrow, next day again the twelve-day-old marrow, and so on until on the tenth day he receives a tenth inoculation from the five-day-old marrow. This is the last, and his treatment is therewith ended. This *simple treatment* is the same for all persons bitten *through their clothes*, which have necessarily wiped the teeth of the animal before they reached the skin. Such bites are oftenest on the legs, arms, or trunk.

If the patient has been bitten on the hands or bare feet, or on any bare region of the body except the face and head, the habitual treatment consists in one series of inoculations, from fourteen to five inclusive, as in the former case, but the viruses

from No. 10 or thereabout upwards are injected twice each, once in the morning, at eleven o'clock, and once in the evening of the same day, at nine o'clock. If the bites be particularly numerous or deep, the patient may be placed in the next category.

Those who have been bitten on the face and head receive the *intensive treatment* proper. They receive the first ordinary course of treatment, rest a day or two; then a second course, rest again; then a third course; sometimes even a fourth course, if the bites are very severe, repeating each one of the stronger injections twice, as above. The second and third courses generally consist of the marrows from No. 10 to No. 5 only, and do not begin with No. 14 as did the first course. In cases of excessive gravity fresher marrows are also used, viz. Nos. 4, 3, 2. During the first months of the new method the simple treatment was the only one employed for all cases. On studying the results of the first year's treatment, it was found that there was a larger number of failures for the hot summer and autumn months than for the winter ones, and a comparative study of the marrows showed that the summer ones of the same date of desiccation were weaker, less virulent, than the corresponding winter marrows. Accordingly,

in the second year of the treatment, fresher, younger marrows, were used in hot weather, and the statistical results were at once improved. They are much better still for this second year (Dr. Roux) than for the first one, which in the main, however, we shall use for our calculations. So also in Odessa, the last improved system of inoculations has proved uniformly successful in more than 550 cases;[1] so Dr. Odo Bujwid, of Warsaw, announces nearly 200 cases of uniform success, most of them now past the period of maximum danger. In the next section we shall see comparative results of the simple and the intensive treatments.

The treatment is gratuitous to all, irrespective of nationality. The only condition is that the applicant shall give reasonable evidence that he has been bitten by an animal which can be fairly suspected of rabies. This generous and excellent arrangement is made possible owing to the Government grant partly, but more especially owing to the proceeds of a permanently open list for public subscription.

The general management of the Pasteur Institute is entrusted to the able care of Professor Grancher.

[1] In Odessa all patients treated are kept in hospital, quiet and at rest for about a month after the treatment is ended.

M. Pasteur, when present, occupies himself chiefly with the registers, and sometimes calls in the patients himself. He never performs the inoculations, and thus remains within legal limits, seeing that he has not got a medical diploma, although a member of the Academy of Medicine. This remark disposes of the ill-tempered note of a medical gentleman who complained rather loudly that the inoculations had been performed on the patients he brought over to Paris 'by an assistant,' only; that 'assistant' must have been either Dr. Roux, the official vaccinator, or Professor Grancher himself.

Statistical Results.

In the first chapter of this work we saw that 20 per cent. was an altogether moderate estimate of the death-rate for all persons bitten by rabid animals, not wolves, taking the cauterised and non-cauterised all together. We shall use it as a basis for our calculations. Similarly, the death-rate after wolf-bites can be put down at 65 per cent., and the percentage after bites on the face and head was shown to be as high as 88 per cent. We shall, as far as possible, compare the first two items with the similar ones

furnished by the statistics of the Pasteur Institutes, wherever such have been founded, and so far as we have been able to collect documents. We shall next examine with some minutiæ the different subdivisions of the statistics supplied by the Central Institute in Paris, dwelling specially on the cases of French or Algerian people, seeing that these have been more thoroughly sifted as to the diagnosis of the rabid or non-rabid condition of the biting animal, and seeing also that their subsequent history after treatment has been on the whole well followed, both by friends and by opponents of the method.

The numbers for the Paris Institute fill up the interval between July 1885 and end of February 1887. The most recent cases amongst them have therefore, by the time we write, got beyond the period of sixty days from the accident, i.e. the period of maximum danger.

So also the cases quoted from Russia, Austria, and Italy have all got beyond the dangerous period, and were treated not less than three months ago.

The deaths of Louise Pelletier and of Moërmann have been previously noticed. M. Pasteur is of opinion that they came too late for treatment, and that they ought not in fairness to be counted as failures of his method. On the other hand, Dr.

Gamaleia, of Odessa, to whom we are indebted for some valuable information, believes that the inoculations are useless if made only a week, or two possibly, before the disease shows itself. There is, then, in his idea what he calls a period of 'nervous incubation'; the poison has already reached the central nervous system and taken possession of it; the vaccinal virus comes too late. There is something very similar to this in the case of variola.[1] All

[1] Dr. Murphy, in his excellent little treatise on 'Infectious Disease and its Prevention,' of the International Health Exhibition Series, says: 'Vaccination passes more rapidly through its various stages than does natural small-pox, and can, therefore, overtake the latter. Vaccination becomes protective when around the vesicle an areola, or ring of redness, has appeared, and this is to be found on the *ninth* day after the performance of the operation. In small-pox, *twelve* days elapse between exposure to infection and the development of the first symptoms; hence, vaccination gains three days upon small-pox, and if performed within the first three days of exposure to infection to small-pox, the latter disease will be prevented. For the knowledge of this fact we are indebted to the late Mr. Marson, who says (Art. "Small-pox," in "Reynolds's System of Medicine"): "Supposing an unvaccinated person to inhale the germ of variola (small-pox) on a Monday, if he be vaccinated as late as the following Wednesday, the vaccination will be in time to prevent small-pox being developed; if it be put off until Thursday, the small-pox will appear, but will be modified; if the vaccination be delayed until Friday, it will be of no use, it will not have had time to reach the stage of areola, the index of safety, before the illness of small-pox begins."'

There seems to be some indication here of a general law that a vaccinal virus runs quicker through its course than the natural virus against which it confers protection.

cases, therefore, in which the disease becomes manifest in one or two weeks after the treatment ought not really, according to that author, to be regarded as failures.

Were we to leave out of count all such cases, the figures would show much more favourably still in favour of the new method. But we shall nevertheless count them as failures, seeing that the full treatment had actually been applied to them. Time and experience can alone decide about these moot points.

	City	Total number treated	Death	Percentage
M. Pasteur	Paris	3,020	34	1·15
Dr. Bujwid. . . .	Warsaw	84	—	—
Prince Oldenburg .	St. Petersburg	140	3	2·14
Dr. Petermann . .	Moscow	112	4	3·57
Drs. Gamaleia and Burdach	Odessa	325	12	3·69
Drs. Cantani and Vestea	Naples	28	—	—
Dr. Ullmann . . .	Vienna	96	—	—
Dr. Parschensky . .	Samara	47	1	2·14
		3,852	54	1·40

Thus, taking all cases together, inclusive of wolf-bites, and inclusive also of those patients who died whilst treatment was in progress, we find a death-rate of 1·40 per cent., with a total of 54 deaths.

Had 20 per cent. of those patients died, the total number of deaths would have been 770 in

r and numbers. By subtraction we find that 726 lives, or 700 roughly, have been saved in less than eighteen months, for the numbers relating to the foreign stations are gathered from the practice of a few months only. And those admirable results were obtained, too, in the first unsettled, tentative period of the existence of the new method, when the simple treatment was applied almost exclusively to even the very worst cases of bites on the hands, face, and head, in the foreign stations in particular. The large proportion of wolf-bites further tends to overload the death-rate.

Wolf-bites. When rabies develops itself after these, it does so in the vast majority of cases before the fortieth day, and often very much earlier. Many of the patients who applied for treatment came after twenty and even thirty days from the infliction of the injury. This circumstance suffices to account for the large number of cases which showed the first symptoms *during* treatment. They number 11 altogether; we leave them out of count in Table B.

A.	In Paris . .	53	cases and	8	deaths
	,, Odessa . .	30	,,	9	,,
	,, Moscow .	18	,,	0	,,
	,, Samara .	4	,,	0	,,
		105		17	

One hundred and five cases, 17 deaths, 16·19 per cent:

B.	In Paris . .	50	cases and	5	deaths
	„ Odessa . .	22	„	1	„
	„ Moscow .	18	„	0	„
	„ Samara .	4	„	0	„
		94		6	

Ninety-four cases, 6 deaths, 6·38 per cent., the usual death rate for such cases being 65 per cent.

PARIS PASTEUR INSTITUTE (alone).

French, Algerians, Foreigners.

Total number of bitten persons treated—

Up to December 31, 1886 . . .	2,682
In January, 1887	162
In February, „	176
Giving altogether . . .	3,020

Out of that number there have died up to this date 34, giving a percentage of dead to bitten of 1·15.

Were severely bitten on the face and head .	242
Of whom there have died	11
Giving a death-rate of	4·58 per cent.

Out of those 242 victims, 213 had been bitten by animals recognised to have been mad by inoculation experiments (A), or certified so by veterinary surgeons (B).

Thus, A and B together give	213
Of whom there have died	11
Giving a death-rate of	5·16 per cent.

Similarly, out of the total number 3,020, the two categories A and B give together .	2,468
Of whom there have died	32
Giving a death-rate of	1·29 per cent.

Class A alone (animals demonstrated mad) gives	293
Of whom there have died	4
Giving a death-rate of	1·36 per cent.

Class B alone (animals certified mad by veterinary surgeons)	2,175
Of whom have died	28
Death-rate	1·28 per cent.
Class C alone (animals suspected of having been mad)	552
Have died	2
Death-rate	0·36 per cent.

Frenchmen and Algerians alone.

Total number treated	2,162
Died	20
Death-rate	0·92 per cent.
Class A	186
Died	3
Death-rate	1·61 per cent.
Class B	1,568
Died	15
Death-rate	0·95 per cent.
Class C	408
Died	2
Death-rate	0·49 per cent.
Classes A and B together	1,754
Died	18
Death-rate	1·02 per cent.

Bites on face and head (usual death-rate 81 per cent.).

Total	242
Died	12
Death-rate	4·95 per cent.
Classes A and B together	213
Died	11
Death-rate	5·16 per cent.
Class C	29
Died	1
Death-rate	3·41 per cent.

Bites on the hands (usual death-rate 67 per cent.) now fall down to 1·22 per cent., bites on the trunk only giving a death-rate of 0·66 per cent.

Both are calculated from Tables A and B together, from a total number of 2,682 patients.

Foreigners treated in Paris.

Total number	858
Died	14
Death-rate	1·63 per cent.
Class A	107
Died	1
Death-rate	0·93 per cent.
Class B	607
Died	12
Death-rate	1·97 per cent.
Class C	144
Died	1
Death-rate	0· per cent.
Classes A and B together	714
Died	13
Death-rate	1·82 per cent.

All the following tables refer to persons whose treatment was finished at least four months ago, and for the great majority of them more than six months ago. They number altogether 2,682.

Out of that number, 49 per cent. had been cauterised one way or another before presenting themselves at the Pasteur Institute.

In 122 cases the bites were cauterised with the

hot iron less than one hour after the accident. Still, these cases gave three deaths. In all three the bites had been very deep and multiple, and in two of the three cases they were on the face.

In 299 cases the hot iron was applied more than one hour after the accident. There were two deaths.

Chemical agents were used as caustics in 794 cases; these gave 14 deaths, i.e. 1·76 per cent. In 107 of the cases the caustics were applied shortly after the bites. In 687 cases they were applied in an altogether inefficient manner.

Total number of cauterised patients treated.	1,216
Of whom there died	20
Death-rate	1·64 per cent.
Total number of non-cauterised patients treated	1,468
Of whom there died	13
Death-rate	0·88 per cent.

The heavier death-rate among the *cauterised* is explained by the fact that the cauterisations are often too slight and applied too late after the accident, coupled with this consideration, that only those persons who have received severe bites have them cauterised at all.

COMPARATIVE RESULTS OF THE SIMPLE AND THE INTENSIVE METHODS.

Simple Treatment.

Classes A and B together	1,649
Of whom there died	26
Death-rate	1·57 per cent.
Class C	443
Died	1
Death-rate	0·22 per cent.

In class C, 409 patients were treated more than four months ago, 34 more than two months ago.

Bites on face and head, total	136
Have died	10
Death-rate	7·35 per cent.

Intensive Treatment.

Classes A and B together	515
Have died	5
Death-rate	0·97 per cent.
Class C	109
Died	1
Death-rate	0·91 per cent.
Bites on face and head, total	50
Have died	0
Death-rate	0

If, however, we carry on the statistics two months further for the last paragraph on bites on face and head, i.e. to two months from the time we are writing, we find :

Bites on face and head (intensive treatment)	78
Has died	1
Death-rate	1·28 per cent.,

which is a much nearer expression of the truth

than the preceding death-rate of zero per cent., which would tend to put down the intensive method as infallible, which we know not to be the case. As it is, the difference between 1·28 per cent. and 7·35 per cent. is sufficiently demonstrative as to the comparative efficiency of the two methods generally.

In July 1886 Professor Grancher made an extremely interesting comparison between the vaccine-viruses of small-pox, of splenic fever, and of rabies as to their relative efficacy. We copy it textually. The numbers for rabies might to-day be slightly modified, but the general indication would still remain the same, and that is the only point of importance. Thus:

Small-pox (from Dr. McCombie's Statistics).

Deaths before Jennerian vaccination .	500 in 1,000
,, after ,, ,, . .	23 ,, ,,
Absolute preservative power of vaccination,	$\frac{500}{23}$ i.e. 21·70

Splenic Fever (figures gathered from statistics furnished by over two hundred veterinary surgeons).

Deaths before Pastorian vaccination .	120 in 1,000
,, after ,, ,, . .	5 ,, ,,
Absolute preservative power . . .	$\frac{120}{5}$ i.e. 24

Rabies (figures from the statistics of M. Leblanc and of M. Pasteur).

Deaths before Pastorian vaccination .	160 in 1,000
,, after ,, ,, .	7 ,, ,,
Absolute preservative power . . .	$\frac{160}{7}$ i.e. 22·85

The numbers 21·70, 24, and 22·85 are extremely striking by their similarity, and look more like the result of some law, as yet unformulated, than that of a mere coincidence.

Some time ago Dr. Domingos Freire, of Rio Janeiro, announced the discovery he had made of a method of prophylactic vaccination against yellow fever. Drs. Paul Gibier and C. Rebourgeon, scientific gentlemen of note, lent him their assistance, and 6,524 persons were vaccinated from January 1885 to September 1886. During the same period there were 1,675 deaths from yellow fever, and of those 1,667 among the non-vaccinated and only eight among the vaccinated. Basing their calculations on a total number of 160.000 individuals exposed to take the disease, they find the death-rate from it to be—for the non-vaccinated, 1 in 10: for the vaccinated, 1 in 100. Thus:

Death-rate for the non-vaccinated . .	100 in 1,000
,, ,, vaccinated . . .	10 ,, ,,
Absolute preservative power . . .	$\frac{100}{10}$ i.e. 10

Dr. Freire's system is much the same as the one employed for the vaccination of cattle against splenic fever. We have here, perhaps, a first extension to other human diseases of M. Pasteur's first results in the study of virulent maladies. His new dis-

coveries teem with all-important deductions, both practical and doctrinal, which we cannot even attempt to point out here.

We may now make a few remarks which spring naturally from what we have seen thus far.

Thus, the death-rate for foreigners, 1·63 per cent., is higher by 0·71 per cent. than the death-rate for French people, 0·92 per cent. The difference must be due, in some degree at least, to the fact that the latter, having shorter distances to travel, can come for treatment earlier after the accident than foreigners.

Considering the Paris Institute alone, we find 3,020 cases and 34 deaths. Now, out of those 34 casualties, no less than one-half occurred in children or youths under eighteen, and that generally in the course of the second month after they were bitten. As we know, the incubation is considerably shorter in children than in adults, and if it should turn out that we must also take into consideration the period of 'latent nervous incubation' of Dr. Gamaleia, it will become more urgent than ever to treat children early after the accident; perhaps, also, will their small doses of prophylactic virus have to be increased. The last-named author seems to say so in connection with his new theory

as to the mode of action of the inoculations. He believes that the vaccinal matter in them is not a dead chemical substance, but actually the living but weakened germs. The amœboid white blood-corpuscles absorb and digest those live germs, and their power of absorption for germs is trained and increased by the progressively stronger inoculations, so that, finally, the virus deposited by the rabid animal can also be absorbed and destroyed. The whole process is carried out, therefore, in the lymphatic system.

This theory of acquired immunity against virulent diseases by destruction of the infecting germs by 'phagocytes' was first put forward by Professor Metschnikoff, of St. Petersburg (see 'Fortschritt der Medicin,' No. 17, 1885, or the 'Revue Scientifique' of May 29, 1886, also Dr. Gamaleia's article in No. V. of the 'Annales de l'Institut Pasteur'). Four more were old people over sixty years of age.

With regard to the relative frequency of bites by different animals, out of a total of 795 cases, gathered exclusively from Western Europe and Algeria, we find that the biting animals were:

Dogs	743 times
Cats	34 "
Wolves	7 "

Oxen	4 times
Donkeys	4 „
Foxes	2 „
Jackals	1 „
Horses	0 „

In Russia, the relative proportion of wolf-bites to others is much greater than in the rest of Europe.

The normal monthly number of patients treated and added to the list averages 160 or rather more, and the new deaths to be added to the dead-list is also found to oscillate monthly within a few units; thus in January there were two deaths, in February and in March none at all, to be added to the statistics closing the year 1886; but there was one belonging to the cases of the preceding month, both in February and in March—it thus becomes easy to foresee that the future statistics will, at the worst, be very much like the past ones. We say at the worst, for the cases are now better understood as to their gravity and the treatment suitable for each, and more experience has been accumulated and will be brought to bear in favour of the patients; the public are also, most important of all, becoming aware of the necessity of early treatment. At page 21, quoting from Professor Brouardel's dictionary article, so replete with well-studied facts, we saw

that 'rabies supervenes oftenest in the course of the second month after infection, rarely after the third month, quite exceptionally after the sixth month.' Now, out of the 3,020 cases we are examining, no less than 2,844 have got beyond the period of three months, and considerably more than 2,000 have got beyond the period of six months. The percentage furnished by those two categories may well, therefore, within perhaps a few decimal points, be considered as fixed and settled. It does not differ sensibly from the general percentage, which we saw to be 1·15.[1] By putting it down at 2 per cent., we are probably misrepresenting the new treatment, and yet it is still then saving 18 lives out of every 100, if we go by the general percentage of 20 per cent. for people who have not received the inoculative treatment.

It has been objected that the majority of people treated at the Pasteur Institute had not been bitten by mad animals at all. Never had any one dreamt of the existence of so many victims of rabid dogs.

[1] These lines and figures were written three months ago. To-day (end of July) they still remain perfectly correct. Both in April and in May there were only two more deaths to be added to the foregoing lists. Dr. Roux is of opinion that for the second year of the treatment the general death-rate will be less than 1 per cent.

Never, too, had any one suspected the existence of such a large number of atrophic bone affections in the course of locomotor ataxy before Charcot first pointed them out; and people still remember that the same objection was urged against Sir Spencer Wells, Mr. Lawson Tait, Dr. Keith, and others; and yet it must have been very difficult for them to invent ovarian tumours. They simply were the right men, able to treat the affection successfully, and the patients took care to find them out. So also M. Pasteur for rabies. Numerous other instances might be adduced, but it is needless to do so. The objection is evidently groundless for classes A and B, and the two together comprise by far the majority of the total number treated. It is doubtful, too, whether the old statistics from which we deducted the different death-rates before the institution of the Pastorian treatment were made with more sifting care than the recent ones. We should say not; and Professor Brouardel has shown that one-third of the departments of France had never sent in reports about hydrophobia, and never figured in the old general statistics.

The opponents of the system grant that the *simple treatment* is harmless in itself, but the *intensive treatment*, say they, is positively dangerous.

Persons who have submitted themselves to it have died of paralytic rabies, a disease which was unknown in man hitherto. It must, therefore, be a new disease, the result of the inoculations they received with the marrows of the paralytic rabbits—an artificial, laboratory rabies. In answer, it is not out of place to remark that the same rabbit-virus injected into dogs oftenest gives rise in them to furious rabies. The two forms of rabies depend in dogs on the seat of the inoculations much more than on the nature of the particular virus inoculated. So that it is really a fresh case of *post hoc, propter hoc*, and at the best *not proven*. Furthermore, some of the patients who died of rabies after the treatment did, as a matter of fact, show some symptoms of paralysis; but, as we saw in the first chapter, paralytic rabies is not by any means a new disease in man. It had simply been overlooked by modern inquirers until the renewal of interest in the whole question elicited closer study. Then again, the mode and seat of inoculation, the quality and quantity of the virus inoculated, being always the same for man, and the virus always taken from paralysed rabbits, we fail to see why the human victims should, in the majority of cases, have died of furious rabies, and occasionally only of paralytic rabies.

In a few cases it has been possible to inoculate into rabbits, after trephining, portions of the central nervous matter of persons who had died of rabies, or who were reported to have died of rabies, after treatment. From experiments which we have previously had occasion to refer to, these rabbits ought to take rabies on the seventh day, on the assumption that the patients had died of laboratory rabies in consequence of their treatment. In one instance two rabbits were inoculated. One of them died of septicæmia in a few days; the other one survived and did not take rabies at all. Still the patient is counted in the dead-list as a case of failure of the method. In another instance the rabbits only developed rabies on the sixteenth day after inoculation, the normal time for them to do so after inoculation with the virus of ordinary canine madness, from which, as thus proved, no doubt the man had died. We have here good evidence that the treatment remained harmless for some unknown reason, although inefficacious.

A good deal was said and written against the new treatment on the occasion of the death of an Englishman, Arthur Wilde, who had been treated in Paris. It was even asserted in several well-known papers, political and medical, that portions

of the medulla and brain of that man had been inoculated into rabbits by Professor Horsley, and that the animals had died of rabies 'on the seventh day' after inoculation. The *death on the seventh day* of the animals was a very suspicious statement, *à priori*. Through the kindness of a common friend, Dr. Anderson, of Paris, we wrote to Professor Horsley, and were favoured with the following information:—

'No one tested Wilde's medulla, unfortunately; he was buried on the doctor's certificate of pneumonia, and so the experiments were not made.' We fully concur in the eminent Professor's expression of regret, but are not sorry to have elicited the truth on the alleged test-inoculations.

Until the present day, then, it may be asserted that in no one single case has it been proved that the treatment was the cause of death in any degree.

But we may, on that very important question, for one moment, and for the sake of argument, grant the otherwise inadmissible supposition that some of the deaths, nay, that every one of them, was due to the treatment itself. What then? It has produced 1·15 death per cent., but at the same time has done away with the old death-rate of 20 per cent. It is, in our supposition, an evil, but a

less one, by far, than was the ancient system, and of two evils by all means let us choose the less and still continue to treat our patients after the new rules.

It has been asserted that the number of persons who do actually take hydrophobia and die after bites of mad animals is extremely small. The assertion is based on statements made by M. Leblanc, of the French Academy of Medicine, and on those, as alleged, of John Hunter. As a matter of fact, M. Leblanc's statistics show a death-rate of 15 per cent., calculated from a total of thirty-six cases only, all the animals *certified* mad by veterinary surgeons, and therefore belonging to class B. If we now go back to the statistics closed at the end of December 1886, and dealing therefore exclusively with patients who have all got beyond the period of four months, and the majority of them beyond that of six months from the time when they were bitten, we find 233 patients who were treated at the Pasteur Institute and who had been bitten by animals *demonstrated* mad by the process of test-inoculation into rabbits of portions of their medulla oblongata, or else by the development of rabies in persons or in animals bitten at the same time but not treated. Out of that considerable number only four have died, giving a death-rate of 1·71 per cent. These

last statistics are extremely significant, and the best we know of in favour of the Pastorian treatment. They are superior to M. Leblanc's figures in every respect: in the certainty of the diagnosis of rabies in the biting animals, in the total number of patients, in the clear statement of the time elapsed since the occurrence of the accident, and above all in the mortality per cent. Were we to apply to them the low death-rate found by M. Leblanc, instead of four deaths we should have had thirty-five.

We have failed in our endeavours to find out statistics referring to rabies in the writings of John Hunter. He only states that the deaths are occasionally very few after the bites of rabid dogs, and quotes the best case he knows of in that respect, viz. twenty persons bitten by the same mad dog and only one death supervening among them; no other details are given.[1] It would be impossible to

[1] 'Dogs are much more susceptible of the infection than the human species. Four men and twelve dogs were bitten by the same mad dog, and every one of the dogs died of the disease, while all the four men escaped, though they used no other means of prevention but such as we see every day to fail. There is also an instance of twenty persons being bitten by the same mad dog, of whom only one had the disease.'—'Observations and Heads of Enquiry on Canine Madness,' in Transactions of a Society for the Improvement of Medical and Chirurgical Knowledge, p. 302. London, 1793.

put down a percentage from that one exceptional and incompletely reported case, and it is to be regretted that the old master did not think it worth his while giving figures in the course of his otherwise excellent paper, which shows undeniably that he knew, a hundred years ago, quite as much about rabies, practically, as we did ourselves until the last few years.

Another circumstance, frequently urged as a radical objection against the new treatment of rabies, is, that the inoculations are not followed by fever, by a mild or a modified attack of the disease, and therefore they must be useless. We completely fail to see the binding force of the argument. Rabies, it ought to be remembered, is not a febrile exanthematous disease of the type of small-pox, typhoid or scarlet fever, and the inoculations have little in common, except the result, with the vaccine-lymph. Why should a forced assimilation be attempted, failing which the inoculations shall be deemed worthless? The fresh rabid nervous matter inoculated on the brain of animals leaves them quite healthy for a time; why should the attenuated, pure viruses give rise to fever in man? Then again, the inoculations are made with the same identical material which is the agent of natural rabies; not so with

vaccine and small-pox; and we know that the inoculation of the virus by the bite of a rabid animal does not for a long time produce any fever or any other appreciable symptom. Why should the same virus, attenuated, be expected to give rise to fever, when introduced into the economy? Similarly, too, natural infection with the germs of many other virulent diseases passes completely unperceived until they have gone through a certain process of development and the malady itself breaks out—syphilis, typhoid, &c. When their attenuated and graduated viruses are in use, some day, we shall probably find that they also do not give rise to fever. We have no doubt that if the vaccine-lymph of small-pox were artificially attenuated and vaccination effected with progressively stronger lymphs instead of the unique strong one, there would be no signs of general reaction at all. Perhaps the vaccination for small-pox will be some day the exception having to be explained—in the way we have just indicated, possibly—and the apyretic inoculations will remain the general and natural type.

It would be out of place on this occasion to enter into considerations as to the mode of production of fever; but we may content ourselves with remarking that it is excessive in some people to argue that, so

long as the absence of febrile reaction after the inoculations has not been clearly explained, they must be considered as unsafe, irrational, unscientific, &c. It is not by the presence or absence of fever that we are enabled to judge of the final results of M. Pasteur's prophylactic treatment.

In certain rare cases the bitten persons, who had come and received the full treatment, a short time only after the accident, still took hydrophobia and died. The treatment had remained powerless. Those failures can possibly be understood by remembering those exceptional cases in which M. Pasteur found that the *blood* of his hypodermically inoculated animals was virulent. The virus was, in the cases which we are considering, deposited by chance inside some blood-vessel cut open by the teeth of the biting animal, and thus passed directly into the general circulation, and into the central nervous system, so that the prophylactic viruses, although inoculated soon after, came too late to be useful. We must keep in mind in that connection that the bites in almost every one of those cases of failure were situated in the most highly vascular regions —feet, hands, face—or were very deep (wolf-bites). In the ordinary run of cases, the greater part of the virus—not to say the whole—is deposited in

the dermic and hypodermic tissues, whence it penetrates into the lymphatic vessels and is carried into the lymphatic ganglia of the region. Here it is stopped some time—the incubation time—and this delay enables the prophylactic viruses to act efficiently.

Is not the *incubation* of virulent diseases generally simply after all the time occupied by the virus in travelling from the point of inoculation, through the lymphatic vessels and ganglia, into the general blood-stream, when commences the period of invasion proper? In that hypothesis the duration of incubation would be dependent on two factors: (1) the invading micro-organism which passes through with more or less ease according to its shape, size, resistance, &c. (compare the degree of malignancy of new growths and the characters of their cells); (2) the state of integrity or otherwise, pathological or physiological, according to age, youth, or old age of the lymphatic ganglia. The anatomical differences in the ganglia of different individuals may help to explain the varying lengths of incubation of the same disease in different people; perhaps also ought the physiological phagocytic activity of the leucocytes to be taken into account.

The question of cruelty to animals has been loudly raised, in England in particular, and has led to incredible excesses of language. We shall not deal at length with it, and shall simply declare that we have plenty of sympathy with the animals sacrificed, but none at all with their short-sighted, weak-hearted, would-be defenders, who would gladly leave thousands of human beings, many of them children, to die from the most horrible death, and thousands more to mourn and suffer, in order to save, until to-morrow, the lives of rabbits. Which is the worse, cruelty to animals or cruelty to man?

M. Pasteur had vaccinated dogs which he afterwards exposed to the bites of rabid animals and found to remain refractory to rabies for several years in succession; so also he had vaccinated and saved animals which had already been bitten. Going further in that line of research, he had trephined and inoculated on the brain a number of animals. By this method every animal inoculated unfailingly takes rabies and dies. And yet he announced that he had been able to save several of them by a process of vaccination with the desiccated marrows going up to and including the first day one, the whole series being injected rapidly in one

day. Several investigators took up the experiments anew. Professor Abreu in Portugal, Renzi and Amoroso in Italy, Von Fritsch in Vienna, failed to obtain similar results. The last-named author has not yet published the full account of his experiments, but another simple statement of fact will weigh heavily against them: Dr. Bardach, of Odessa, trephined and inoculated on the brain twenty-one dogs in all. Six of them were kept unvaccinated and soon died of rabies. Fifteen were vaccinated after a few hours by the rapid and intensive method. Five of them still developed rabies and died, but the remaining ten showed no symptoms of the disease and are still kept alive and healthy in the kennel at Odessa—66 per cent. The experiments were made in September and October 1886. It is scarcely necessary to point out again that intra-cranial inoculation is infinitely more dangerous than ordinary bites of mad animals. It is extremely probable that every one of the fifteen vaccinated dogs would have proved refractory to rabies as inoculated by *bites*.

Referring to those experiments M. Pasteur says: 'Dr. Fritsch was wrong probably in choosing rabbits for his experiments. Rabbits may, indeed,

be rendered refractory to rabies, but it is much more useful to deal with dogs.'[1]

[1] Since writing those lines Dr. von Fritsch's Report has been published *in extenso*. According to the best judges it seems very probable that there must have been something radically wrong in his experiments, made chiefly on rabbits. A large proportion of them died of septicæmia; the duration of incubation and various other circumstances varied very largely in different animals—all results which are practically unknown in Paris, or in other places where the experiments proved successful and in keeping with those of M. Pasteur. See criticisms by Dr. Gamaleia in the *Annales de l'Institut Pasteur*; also M. Pasteur's letter to the Vienna Academy of Medicine (June 1887.)

Confirmatory experiments to those of M. Pasteur have also been realised of late by several other investigators: in Turin by Piano and Bordoni Ufreduzzi; in Naples by Vistea; in Vienna by Ulmann; in Warsaw by Odo Bujwid, who even succeeded in vaccinating and saving rabbits after infective inoculations on the brain; by Prof. Ernst, of Philadelphia, with a remarkably large proportion of successful cases out of a total of over thirty experiments; lastly, by Professor Horsley, the Secretary of the special English Commission (of which the other members were: Sir James Paget, Dr. Lauder Brunton, Dr. Fleming, Sir Joseph Lister, Dr. Quain, Professor Sir Henry Roscoe, M.P., and Professor Burdon Sanderson), appointed by the Local Government Board to investigate into the efficacy or otherwise of M. Pasteur's treatment.

The Report of the Committee, presented to Parliament on June 27 last, is a unanimous and complete expression of confidence in M. Pasteur's system. 'The possibility of communicating rabies at pleasure having thus been completely established, the next part of the inquiry had reference to the possibility of affording protection against it to persons or animals who had not yet been bitten, or of preventing its development in those who had been bitten. The former was easily determined by means of animals; and for this purpose, in Professor Horsley's experiments, six dogs were "protected" by injecting under their skins, with an

In Continental countries we shall still have to depend almost exclusively on well-devised and

ordinary needle syringe, emulsions from the spinal cords of rabbits which had died of rabies; beginning with a cord which had been dried for fourteen days, and on each following day using a cord which had been dried for one day less than the preceding, until at last a fresh cord was used. None of these dogs suffered in any way from the injections; and when they were completed, the six dogs thus protected, and two others unprotected, and some rabbits unprotected, were made insensible with ether, and were then bitten by rabid dogs, or by a rabid cat, on an exposed part. A protected dog, No. 1, was bitten on July 8, 1886, by a dog which was paralytically rabid, and it is still perfectly well; while an unprotected dog, bitten on the same day by the same rabid dog, died paralytically rabid. A protected dog, No. 2, was bitten on November 6, 1886, by a dog which was furiously rabid, and has remained well. At the same time four unprotected rabbits were bitten by the same rabid dog, and of these two died of rabies. The same results followed with the protected dog No. 3, and with the unprotected rabbits bitten at the same time. The dog still lives, the rabbits died of rabies. The protected dogs, Nos. 4 and 5, were bitten on January 20, 1887, by a furiously rabid dog; and on the same day the unprotected dog No. 2 and three unprotected rabbits were bitten by the same dog. The protected dogs remain well, the unprotected dog and two of the rabbits died of rabies. The protected dog, No. 6, was bitten on three different occasions by a furiously rabid cat on September 7, 1886, by a furiously rabid dog on October 7, 1886, and by another furiously rabid dog on November 6, 1886. It died ten weeks after the third bite, but not of rabies, as was proved not only by the character of its illness, but also, and conclusively, by the negative result of inoculations performed on two rabbits with an emulsion from its fresh spinal cord. There seems, therefore, to be conclusive evidence that protection against the bite of a rabid animal may be afforded by previous inoculations; and the only remaining question is whether the antidote can be made to overtake the poison when this has

strictly enforced police regulations in order to minimise the risks from rabid animals. We are far yet from having seen the last mad wolf, the last mad fox, or the last mad jackal, and those animals are beyond the reach of the policeman. But a great deal can be done for dogs and for the public by taxing the animals heavily, muzzling them efficiently, and destroying all vagrant curs. The example of Sweden and Norway and of Germany, which have led the way in those respects, is conclusive.

In island countries the vaccination of animals of the canine species every second or third year has been proposed as a help to police regulations. It will perhaps be found advantageous, at any rate, to vaccinate against rabies all valuable dogs, especially if kept in packs.

M. Pasteur's treatment is well styled by himself 'prophylactic.' It is not and does not claim to

actually been introduced. On this point the Committee furnish a very complete analysis of the cases in which preventive inoculation has been practised by M. Pasteur, between October 1885 and the end of December 1886—cases amounting to 2,682 in number, and of which 127 went from this country. They arrive at the conclusion that the inoculations performed by M. Pasteur on persons bitten by rabid animals have prevented the occurrence of hydrophobia in a large proportion of those who, if they had not been so inoculated, would have died of the disease . . . .'—*The Times*, June 28, 1887.

be in any degree curative; it is powerless against the disease when the first symptoms have once made their appearance, and even for a few days before in all probability. Hence the necessity, it cannot be too often repeated, of early treatment. This, coupled with the inability to travel, for some reason or other, of not a few patients, would make it advisable that the central station were able to send out the viruses carefully labelled and accompanied with detailed directions for use by the medical attendant. Telegraph and railway might make some such arrangement possible. For journeys of any length, however, it would become necessary to send the marrows themselves, in glycerine: and then at once the difficulties and dangers of manipulation become too great to be entrusted to an inexperienced person, even though medical, and we should say that the safest and quickest plan will continue to be, for all who can afford to do so, to repair to the central station; it will be good time enough to reach there within one, two, or three weeks after the accident, if the bites are not more than ordinarily severe. But the rule is: *the sooner the better.*

The mother Institute in Paris was for a long time equal to the needs of the whole of Europe, and

even of extra-European lands. It is so still for the whole of France, of the British Islands, of Spain and Portugal, of Western Europe generally, and for most of the countries bordering on the Mediterranean. It will continue to be the Pasteur Institute of all countries which deem it inexpedient to found a special station against rabies owing to the small number of persons bitten in them.

The Buisson treatment, about which there has been much talk of late, claims to be *curative*, and consists essentially in excessive sudation either by immersion in an ordinary hot bath or by means of a Turkish bath, repeated twice or thrice daily until a cure is effected—or the patient dies. Whatever the value of the method, it can lay no claim to novelty, and sudation as a mode of treatment of *confirmed rabies* has been practised for centuries; in particular may we refer to a baker who used to shove his rabid patients into his oven. They came out roasted and asphyxiated, or cured. His memory is immortalised in the 'Petit Albert,' a book of witchcraft of the Middle Ages. The Buisson treatment must be judged by its works. It must furnish us with better statistics than it has done hitherto; it must also explain the disuse into which it has fallen, although it has been known so long.

What, in conclusion, may we prognosticate as to the fate in future of the new method? This, that it will be, modified perhaps, the treatment for hydrophobia as long as hydrophobia itself continues one of the ills that human flesh is heir to. We say so unhesitatingly, because M. Pasteur's discovery is based on well-established experimental facts: because it has shown itself efficient against rabies whilst remaining harmless in itself, so long as handled by careful and experienced hands; because it is so simple in application, whilst throwing so much hope in regions where the wildest despair reigned supreme; because it is an application of the ever-sound principle that prevention is better than cure. In this instance prevention means more than it does usually. Jennerian vaccination prevents small-pox. But many of the persons vaccinated during an epidemic of small-pox would never have taken the disease, although they had been left unvaccinated—or would have taken it in a mild form—because they had already been vaccinated previously, or because they had already had the disease, or because they might have fled to some other country. Not so with rabies. The persons Pasteurised against it, if we may so speak, already have the germ of the malady in their system and are in imminent danger.

and the disease, if it show itself at all, knows of no alternative—it kills, and there is no flight from it anywhere or by any other means. Indeed, some substance or some physical agent may be discovered yet which will have the power of curing the declared disease itself: it will complement, not supersede, Pasteur's treatment, for this reason, that no therapeutic agent, however specific in a given disease, is ever infallible. All patients would still submit themselves to the inoculative treatment, and this failing, for some reason or other, would yet have a second chance of escape from the dread scourge.

One year later, after the demonstration afforded by accumulated evidence from various and independent sources, we may repeat what M. Pasteur already felt justified in saying in his note of March 1, 1886: 'The prophylaxis of rabies after bites is now an established fact.'

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